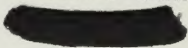







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1985-86, Fall Semester

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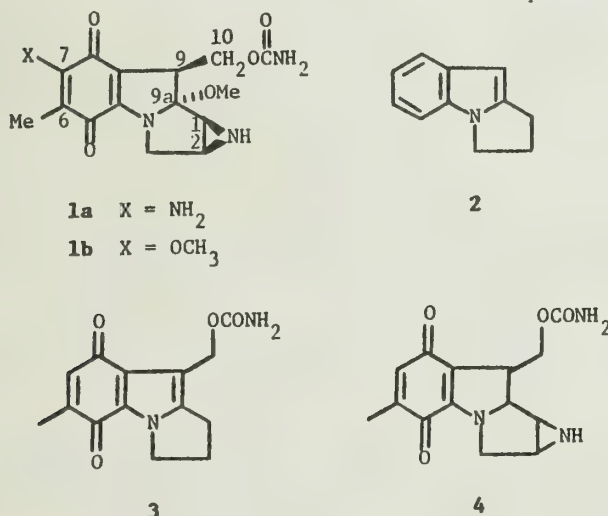


AZIRIDINOPYRROLOINDOLES: MITOMYCIN ANALOGUES

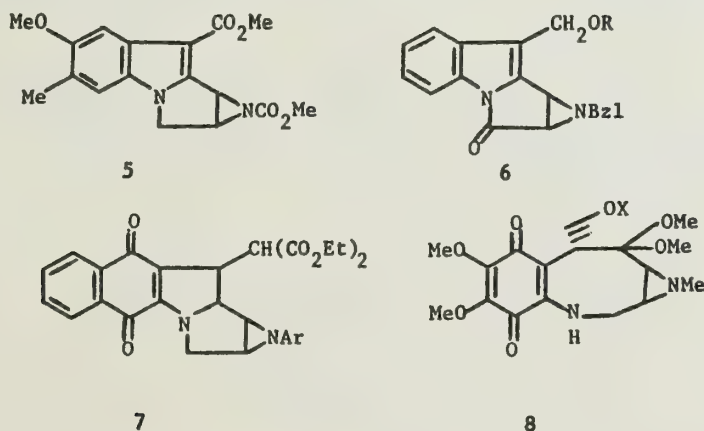
Reported by Terry Moran

September 5, 1985

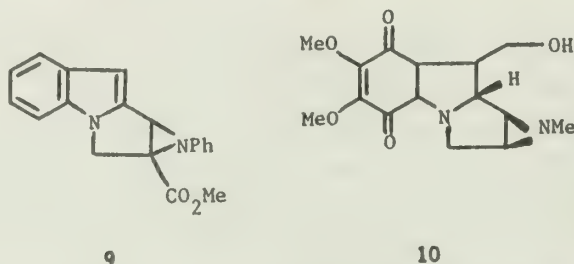
The mitomycin antitumor antibiotics<sup>1</sup> (Mitomycin C, **1a**); Mitomycin A, **1b**) have been the target of many synthetic studies<sup>2</sup> related to the tricyclic 2,3-dihydro-1H-pyrrolo[1,2-a]indole nucleus (**2**) (mitosene, **3**). An effective leaving group at C-1 of the pyrroloindole nucleus, such as the 1,2-aziridino function characteristic of the mitomycins is necessary to allow bisalkylation<sup>3</sup> and for full antitumor activity.<sup>4</sup> Despite the impetus of substantial biological activity for this class of compounds, relatively few syntheses of the tetracyclic 1,2-aziridinopyrrolo-indole nucleus have been completed (mitosane, **4**).



Synthetic methods for the preparation of 1,2-aziridino-pyrroloindoles are varied. Addition of iodine azide followed by reduction, cyclization of the iodoamine an protection afforded carbamoyl aziridine **5** from the corresponding olefin.<sup>5</sup> Cycloaddition with benylazide followed by photolysis to produce **6** has also been successful.<sup>6</sup> A one-pot photosynthetic cyclization resulted in benzomitosene analogue **7**. The unique total synthesis<sup>8</sup> of the mitomycins introduced the aziridine ring in a series of conversions from the corresponding epoxide, with the key step a biomimetic<sup>9</sup> transannular cyclization of benzazocaine **8**.



More recently, an intramolecular Darzen's reaction has been utilized to produce **9** via a bicycloannulation.<sup>10</sup> Further, aziridinomitosane **10** was formed from the corresponding unsaturated mitosane.<sup>11</sup>



Other developments include: i) the preparation of trans 2-aminomitosenes from bioreductive alkylations<sup>12</sup>; ii) the observation of cis and trans products from an elusive, tetracyclic 1,2-epoxypyrrolo-indole intermediates<sup>13</sup>; iii) reductive formation of dihydro(leuco)mitomycins without aromatization.<sup>14</sup>

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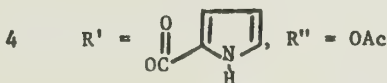
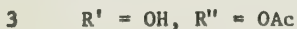
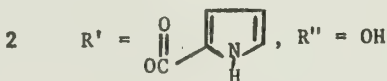
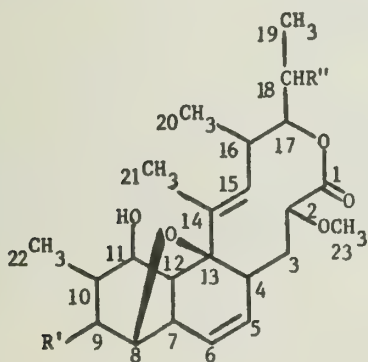
BIOSYNTHESIS OF NODUSMICIN AND NARGENICIN;  
NOVEL MACROLIDE ANTIBIOTICS

Reported by William C. Snyder

September 12, 1985

Recent biosynthetic investigations of reduced polyketide antibiotics have included the avermectins,<sup>1</sup> monensin,<sup>2</sup> and lasalocid.<sup>3</sup> Studies of those compounds representing reduced linear polyketides have suggested that the biosynthetic pathway is quite similar to that known for classical saturated fatty acids.<sup>4</sup> Formation of the more complex carbocyclic ring systems is not as well characterized. Thus, biosynthetic investigations of the novel macrolide antibiotics nodusmicin **1**<sup>5</sup> and nargenicin **2**<sup>6</sup> were conducted. The acetate-propionate origin of the macrolide skeleton was confirmed by <sup>14</sup>C- and <sup>13</sup>C-labeling experiments. The antibiotic complex was first isolated from the fermentation medium by solvent extraction followed by processing over silica gel with a chloroform-methanol step gradient to yield the individual antibiotics. Two new metabolites possessing the cis-octahydronaphthalene ring system were discovered and identified as 18-O-acetylnodusmicin **3** and 18-O-acetylnargenicin **4**. Assignments of **3** and **4** were based on comparisons of the electron impact mass spectra and the <sup>13</sup>C-NMR spectra with authentic nodusmicin and nargenicin.<sup>7</sup>

Additional studies by Cane and Yang<sup>8</sup> involving isotopic oxygen have ruled out the plausible epoxy-alcohol cyclization for formation of the bicyclic ring system. However, the data does not rule out the possibility of an intramolecular Diels-Alder reaction between an E,E-4,6-diene and an E dienophile.



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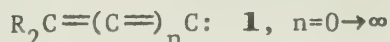


# GENERATION, STRUCTURE, AND REACTIONS OF ALKYLIDENECARBENES

Reported by Douglas A. Burg

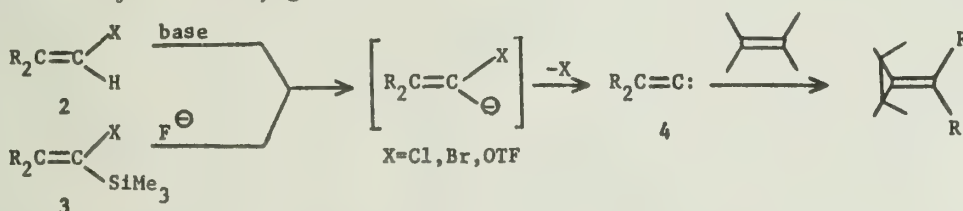
September 16, 1985

Alkylidenecarbenes, **1** ( $n=0$ ), are the simplest members in an infinite series of unsaturated carbenes. Since alkylidenecarbenes are mechanistically interesting as well as synthetically useful, they have been extensively studied in recent years.<sup>1,2</sup>

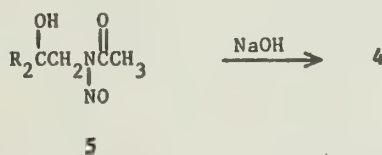


## Generation

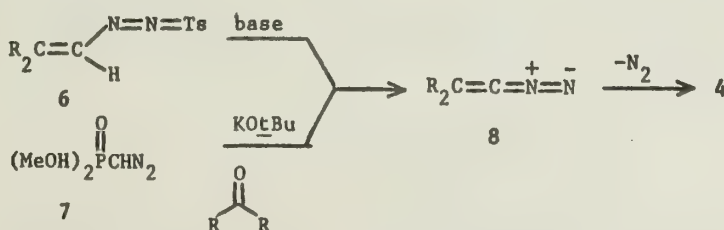
Alkylidenecarbenes may be generated by many of the same methods used to generate alkyl carbenes. Treatment of olefins such as **2** with a base produces the vinyl anion which undergoes an  $\alpha$ -elimination to generate alkylidenecarbenes. Chloride, bromide or triflate ions may serve as the leaving group for formation of the carbene, **4**.<sup>3-6</sup> The vinyl anion may also be formed by nucleophilic attack of fluoride ion on vinylsilanes, **3**.<sup>7,8</sup>



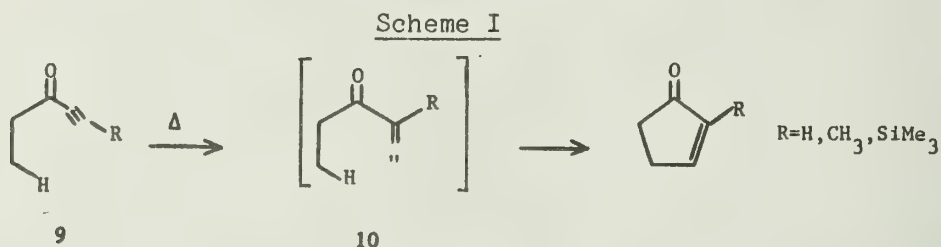
Alkylidenecarbenes can be generated under phase transfer conditions by sodium hydroxide-induced decomposition of N-nitrosoacetyl amino alcohols, **5**.<sup>9</sup> This method produces methylenecyclopropanes in 60-83% yields. Reaction of (tosylazo)-



alkenes, **6**, with amine bases produces alkylidenecarbenes<sup>8</sup> as does base-promoted reaction between dialkyl (diazomethyl)phosphonates, **7**, and ketones.<sup>10,11</sup> In these two methods unsaturated carbenes are believed to form by the loss of nitrogen from an intermediate diazoethylene, **8**.

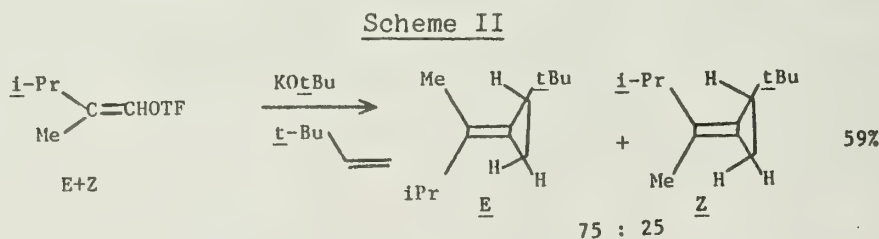


Alkylidenecarbenes have also been generated by the thermal rearrangement of alkynyl alkyl ketones ( $\alpha$ -alkynones, 9). When a  $\beta'$ -hydrogen is present the alkylidenecarbene can undergo intramolecular carbon-hydrogen bond insertion to form cyclopentenones (Scheme I).<sup>12</sup>



### Reactions

Various substituted methylenecyclopropanes can be formed by the addition of alkylidenecarbenes to olefins. When unsymmetrical carbenes and olefins are used the reaction is stereoselective with the E-product predominating, Scheme II.<sup>4</sup>



The stereoselectivity of carbene addition to olefins has been used to establish that alkylidenecarbenes exist in a singlet ground state.<sup>13</sup>

Base-promoted reaction between dialkyl ketones containing at least one  $\gamma$ -hydrogen and dialkyl (diazomethyl)phosphonates produces cyclopentenones in 22-95% yields via intramolecular carbon-hydrogen bond insertion of the intermediate alkylidenecarbene.<sup>11,14</sup>

Flash vacuum pyrolysis of  $\alpha$ -alkynones bearing at least one hydrogen atom in the  $\beta'$ -position leads to 2-cyclopentenones, as shown in Scheme I, in high yields.<sup>12</sup> The alkylidene carbene 10 is a proposed intermediate in this reaction.<sup>15a-c</sup>

The  $\alpha$ -alkynone cyclization has been shown to be synthetically useful in the synthesis of natural products including (+)-clovene,<sup>15d</sup> rac-modhephene,<sup>16,17</sup> a stereoisomer of ptychanolide,<sup>18</sup> and (+)-albene.<sup>19a</sup> A double application of the  $\alpha$ -alkynone cyclization was used to synthesize the tricyclopentanoid (+)- $\Delta^9(12)$ -capnellene.<sup>19b</sup>

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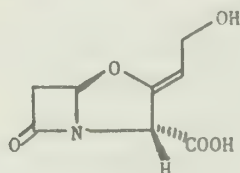
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# BIOSYNTHESIS OF CLAVULANIC ACID

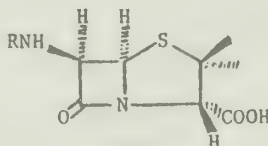
Reported by Martha Schlicher

September 19, 1985

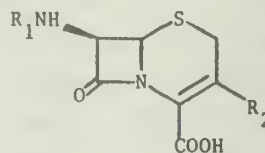
Clavulanic acid 1, a  $\beta$ -lactam antibiotic produced chiefly by *Streptomyces clavuligerus*, exists naturally with the penicillins 2, and the cephalosporins 3, yet is structurally different from both classes.<sup>1</sup> The acid demonstrates broad, low-level



1



2



3

antibacterial activity and potent progressive inhibition of many  $\beta$ -lactamases, preventing the  $\beta$ -lactamase catalyzed ring hydrolysis in both the penicillins and cephalosporins.<sup>2a,b</sup> The synergistic activity of clavulanic acid has recently been exploited by the marketing of the acid in combination with various antibiotics.<sup>1e</sup> As the naturally occurring  $\beta$ -lactamase inactivators have proven to be the most potent, the biosynthetic origin of the clavulanic acid antibiotic has become a topic of current interest and controversy.<sup>1a,3</sup>

Investigation of the biosynthesis of clavulanic acid was initially attempted using carbon-14 precursors; comparing the radioactivity of the precursors versus the products. No significant results were obtained due to minor incorporation of a wide variety of compounds.<sup>3d</sup>

Later work by Elson involved studying the incorporation of carbon-13 labeled precursors. Location of the label was determined by <sup>13</sup>C NMR analysis of the product clavulanic acid derivative, benzyl clavulanate.<sup>3a</sup> These studies appeared to indicate  $\sigma$ -amino-hydroxyvalerate as the origin of the oxazolidine carbon skeleton. The  $\beta$ -lactam carbons were believed to be derived directly from glycerol or generated via gluconeogenesis. Elson confirmed these results by the incorporation of carbon-14 precursors into clavulanic acid followed by degradation to determine the locations of the carbon-14 labels in the products.<sup>3a-c</sup>

Recent work by Townsend studying the degradation of labeled clavulanic acid generated from doubly labeled precursors sheds new light on the earlier carbon-13 and -14 experiments.<sup>1a,3e</sup> These results indicate biosynthesis of the oxazolidine carbon skeleton from the C-5 amino acid, ornithine. In addition, glycerate was identified as the origin of the C-3 unit producing the  $\beta$ -lactam carbons.



The mode of biosynthesis elucidated in these recent results is consistent in part with the method of biosynthesis previously determined for the penicillins and cephalosporins. These antibiotics are entirely amino acid derived.<sup>4</sup>

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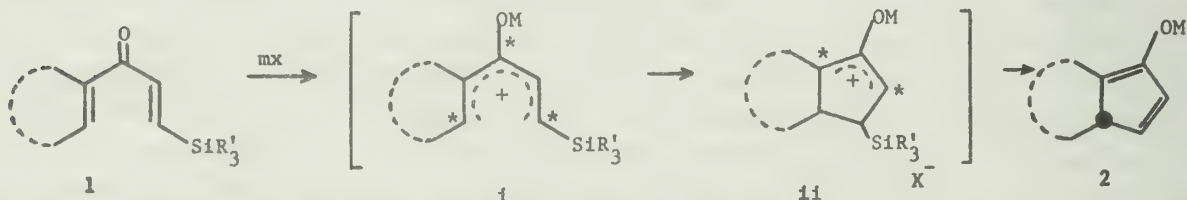
THE SILICON-DIRECTED NAZAROV CYCLIZATION (SDNC): STEREOCHEMICAL,  
MECHANISTIC, AND SUBSTITUENT-COMPATABILITY STUDIES

Reported by Karl Habermas

September 23, 1985

Cyclopentanoid natural products remain popular targets for total synthesis because of their biological activity and synthetic challenge. Cyclopentane rings are found in diverse structural contexts in prostaglandins, polyquinanes, iridoids, pseudoguianes, and ophiobolins. While a number of strategies for their construction have been devised the need remains for general methods.<sup>1</sup> The classical Nazarov reaction,<sup>2</sup> in which divinyl ketones cyclize to afford cyclopentenones, has been modified by affixing a silicon substituent to a vinyl carbon  $\beta$ - to the carbonyl (Scheme I)<sup>3</sup>. This has several interesting consequences: (1) the double bond is

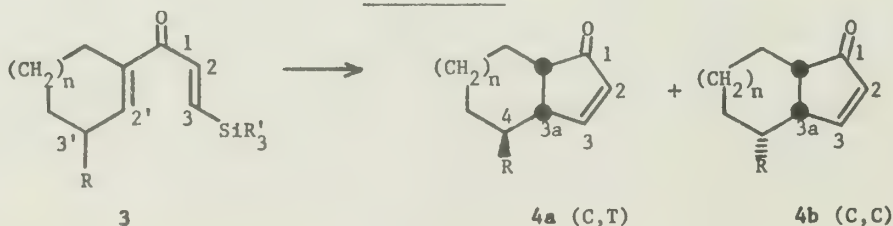
Scheme I



placed in the thermodynamically least favored position, (2) the pericyclic character of the reactions is expressed, the stereochemical outcome reflecting the direction by which conrotatory cyclization occurs and (3) side reactions are suppressed. The potential for stereocontrol with ring substituents of different size and position, and with various silicon ligands, has been addressed. The effects of vinylsilane substituents on the rate and course of cyclization have been investigated. The compatibility of several heteroatom-containing functional groups with the reaction have also been studied.

The cyclization of cyclopentenyl, -hexenyl, and -heptenyl vinyl ketones with a 3'-methyl group and several silicon ligands has been systematically surveyed (Scheme II).<sup>4</sup> The cyclopentenyl vinyl ketone ( $n=0$ ,  $R=Me$ ) bearing a trimethylsilyl appendage

Scheme II



( $R'=Me$ ) cyclized with essentially no stereoselectivity. Incrementally augmenting the bulk of the silicon ligands increasingly favored the C,T isomer (up to 4:1 with

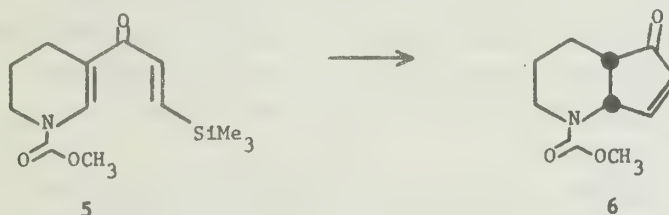


R'=iPr) but with a concomitant decrease in yields. The cyclohexenyl system (n=1, R=Me) proved more amenable to stereocontrol. With the largest silicon ligands cyclization afforded greater than 9:1 predominance of the C,T isomer in good yield. In the cycloheptenyl system stereoselectivity was poor and little affected by the silicon ligands.

In the six-membered ring series larger 3'-substituents (R=Ph, tBu, etc.) greatly enhanced the stereoselectivity of cyclization, invariably favoring C,T product (>9:1).<sup>4</sup>

Divinyl ketones bearing a methyl group at C(3) or an allyl or phenyl group at C(2) of the vinyl silane have been prepared. Silylcupration methods allowed the assembly of the latter in one step.<sup>5</sup> Substituents at C(2) accelerated the cyclization, while substitution at C(3) retarded this process. These results are in accord with theory. The compatibility of the SDNC with oxygen in various positions remote from, appended to, or in the ring has been explored. Substrates with benzyloxymethyl and benzyloxy groups attached to C(3'), as well as 3'-dihydro-pyranyl systems, cyclized in good to excellent yields. When diastereomers may be formed selectivity was very high. Benzyloxy or methoxy attached to C(6'), or oxygen replacing it, gave little or no cyclization product.

A divinyl ketone containing a carbomethoxy-protected nitrogen attached to the carbon of the internal olefin  $\beta$ - to the ketone (5) has been synthesized by an efficient route. Cyclization was greatly retarded by the 3' donor group but occurred in 76% yield with  $ZrCl_4$ . The use of this product as an intermediate in the synthesis of the natural product streptazulin<sup>6</sup> is under investigation. Preparation of the analog with nitrogen connected to the  $\alpha$ -carbon, is now in progress.



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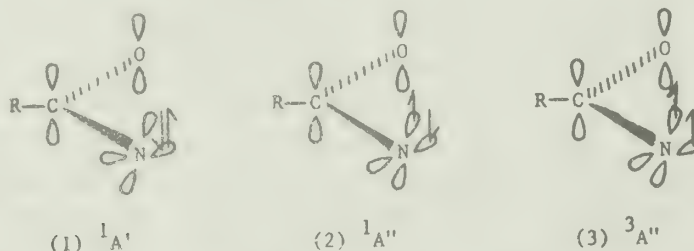
THE CHEMICAL AND PHYSICAL PROPERTIES OF  $\beta$ -NAPHTHOYL AZIDE;  
THEORETICAL VS. EXPERIMENTAL

Reported by Tom Autrey

September 26, 1985

Acyl azides were first introduced to organic chemistry 100 years ago when Curtius demonstrated that thermolysis of acyl azides gave in high yields the corresponding isocyanates.<sup>1</sup> Direct photolysis of acyl azides gives nitrene type products<sup>2</sup> as well as isocyanates, while triplet sensitized photolysis of acyl azides gives nitrene type products and no isocyanates.<sup>3</sup>

Acyl nitrenes, generated by photolysis of acyl azides, are electroneutral, electron-deficient, monovalent nitrogen derivatives. The three low-energy orbitals of acyl nitrenes make possible at least three different electronic configurations; (1) a singlet state,  $^1A'$ , with its spins paired in the same orbital, (2) another singlet state  $^1A''$ , with its spins paired in two different orbitals, and (3) a triplet state,  $^3A''$ , with its spins unpaired.

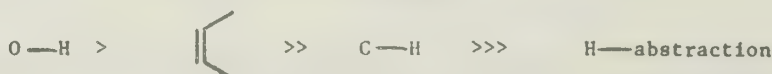


Theoretical calculations predict the parent acyl nitrene, formyl nitrene, (R=H), to be a ground state triplet with two closely spaced singlets more than 30 Kcal/mole above the triplet.<sup>4</sup> The calculations indicated that the R-group is essentially unconjugated with the N-atom and would not alter the energy gap between the singlet and triplet states.

Recent experimental evidence seems to indicate otherwise. Photolysis of benzoyl azide under direct or triplet-sensitized conditions in the presence of cis-or trans-1,4-dimethylcyclohexanes gave the insertion product (tertiary benzamide) stereospecifically, an expected singlet reaction.<sup>3a,5</sup>

Photolysis of  $\beta$ -naphthoyl azide in a variety of solvents gives an essentially constant yield, 50%, of  $\beta$ -naphthyl isocyanate and a 50% yield of nitrene type products. The relative reactivity of the generated nitrene towards these solvents is shown in Scheme 1. The electrophilic character of the intermediate is in accord

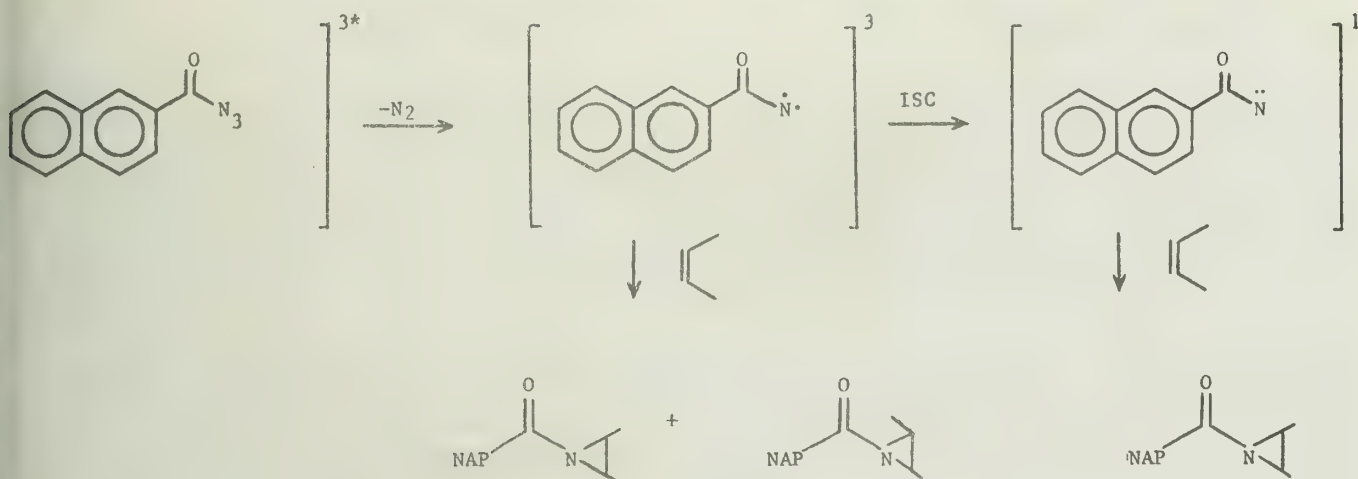
Scheme I



with expectations for a singlet nitrene. Triplet-sensitized photolysis of  $\beta$ -naphthoyl azide in the presence of 4-methyl-cis-2-pentene gives only



cis-aziridine. A ground state triplet nitrene would be expected to give a mixture of isomers.



The experimental evidence in support of ground state singlet acyl nitrenes<sup>6</sup> indicates that new calculations need to be performed. A useful application of these very reactive acyl nitrenes could be their use as photoaffinity labeling agents.<sup>7</sup>

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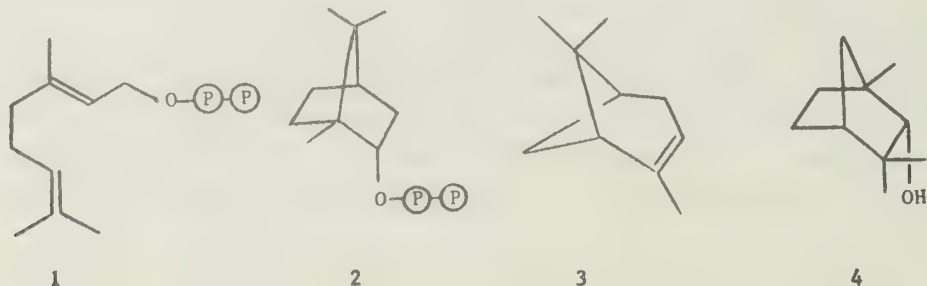
# SPECIFICITY IN MONOTERPENE BIOSYNTHESIS

Reported by Jon Denissen

September 30, 1985

The monoterpenes, ten-carbon members of the terpenoid class of compounds, were the first group of isoprenoids to be thoroughly investigated from a chemical standpoint.<sup>1</sup> However, the biochemistry of these compounds remains largely unknown, trailing behind current biochemical knowledge of higher terpenoids such as steroids and carotenoids. Several early studies of monoterpene biosynthesis were complicated by compartmentalization effects, phosphohydrolases and insufficient product purification. Many of these studies are now considered invalid,<sup>2</sup> while most accepted *in vivo* tracer studies served only to delineate biogenetic pathways leading from labeled precursors to labeled monoterpene products.<sup>3</sup> However, recent isolations of several cell-free monoterpene enzyme cyclases have allowed the examination of regiospecificity, stereospecificity, and the nature of reactive pathway intermediates involved in monoterpene biosynthesis.<sup>4</sup>

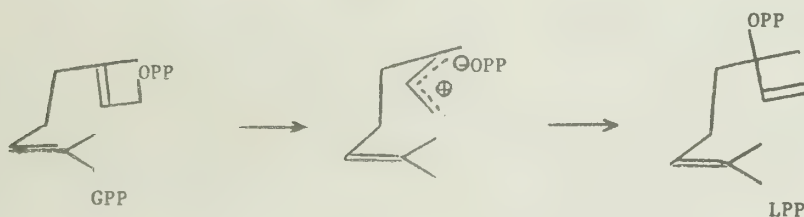
Three of the best understood cell-free enzyme cyclase systems isolated to date are the bornyl pyrophosphate cyclases, the pinene cyclases and (-)-*endo*-fenchol cyclase. The bornyl pyrophosphate cyclases have been isolated from sage (*Salvia officinalis*) and tansy (*Tanacetum vulgare*) and catalyze the  $Mg^{2+}$ -dependent conversion of geranyl pyrophosphate 1 to the (+)-(sage) and (-)-(tansy) enantiomers of 2-bornyl pyrophosphate 2.<sup>5</sup> The pyrophosphate antipodes are converted by a hydrolase<sup>6</sup> to the corresponding bornyl enantiomers, which are, in turn, converted by a dehydrogenase to the respective camphor enantiomers in intact plant tissue.<sup>7</sup> Pinene cyclases I and II have been isolated from sage (*Salvia officinalis*) leaves and catalyze the  $Mg^{2+}$ -dependent cyclization of geranyl pyrophosphate to  $\alpha$ -pinene 3 and camphene, limonene,  $\beta$ -pinene and myrcene. Pinene cyclase I produces only the (+)-isomers of  $\alpha$ -pinene, camphene and limonene, while cyclase II gives only the (-)-antipodes, along with (-)- $\beta$ -pinene and myrcene.<sup>8</sup> (-)-*endo*-Fenchol cyclase, obtained from fennel (*Foeniculum vulgare* M.) leaves and fruit, catalyzes the  $Mn^{2+}$ -dependent conversion of geranyl pyrophosphate to (-)-*endo*-fenchol 4, which is subsequently dehydrogenated to produce (+)-fenchone.<sup>9</sup>





All of these cyclases prefer geranyl pyrophosphate, despite the trans double bond at C2 of GPP that prohibits direct cyclization. They can also utilize the neryl and linalyl analogs as substrates. Furthermore, all cyclizations occur without detectable free intermediates. Based upon observed product distributions, analogous higher terpenoid mechanisms,<sup>10</sup> and chemical model studies,<sup>11</sup> a mechanistic scheme for monoterpene cyclizations invoking geranyl pyrophosphate isomerization to an enzyme-bound linalyl pyrophosphate intermediate has been advanced (Scheme 1). This seminar will describe recent investigations into the regio- and stereospecificity of these enzymatic conversions that lend support to the current mechanistic proposal.

Scheme I



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# RECENT DEVELOPMENTS IN REGIO- AND STEREOCONTROLLED 1,4-HETEROATOM ADDITION TO CONJUGATED DIENES

Reported by Wei Dai

October 7, 1985

Many synthetic endeavors require stereoselective 1,4-diheteroatom-substituted-2-alkene derivatives as intermediates<sup>1</sup> (Fig. 1). A direct route to such compounds is 1,4-addition to conjugated dienes. Four major methods for the 1,4-addition have

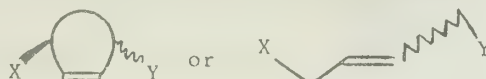
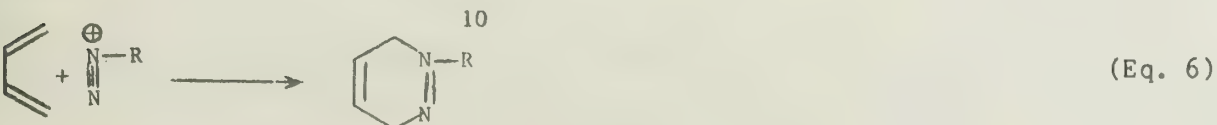
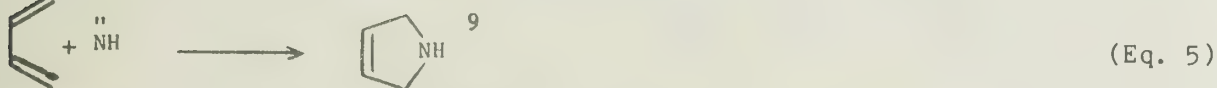
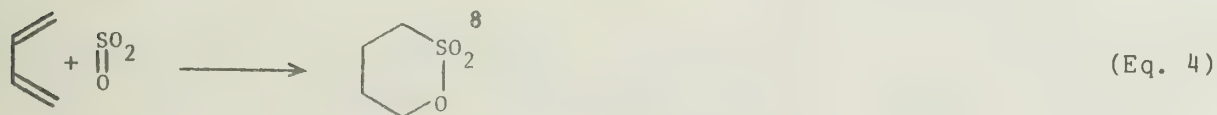
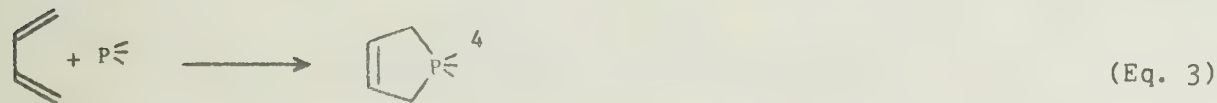
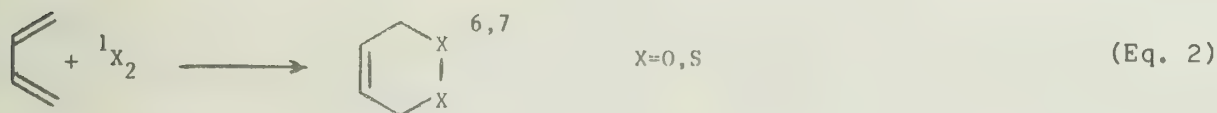
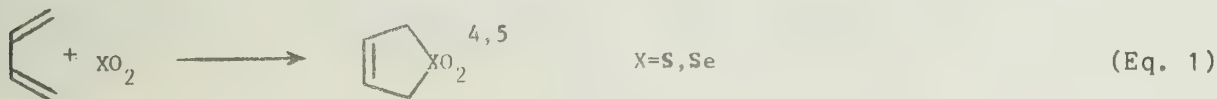


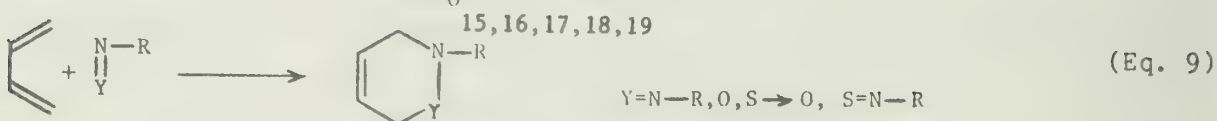
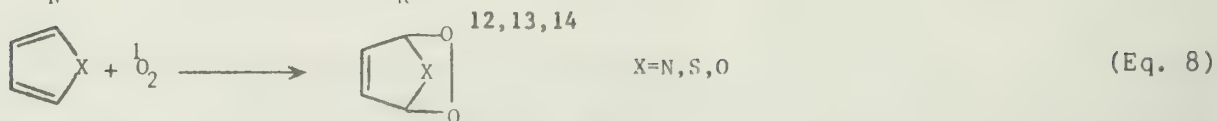
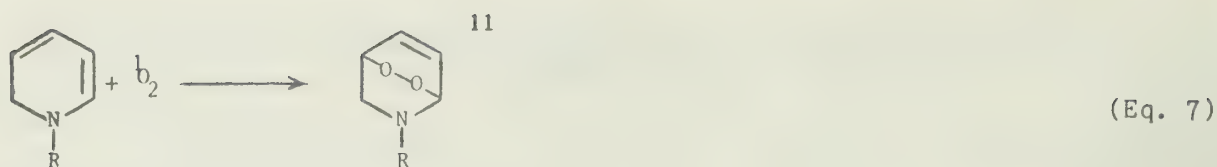
Figure 1. General Structure of 1,4-diheteroatom-2-alkene

been developed: (1) electrophilic addition, (2) free radical addition, (3) 1,4-cycloaddition, and (4) nucleophilic addition. Since the electrophilic and radical additions lead to either a multiplicity of products,<sup>2</sup> or a lack of stereoselectivity,<sup>3</sup> respectively, this report will emphasize the latter two methods which have been developed recently.

## 1,4-Cycloaddition Reaction

The initial method for regio- and stereoselective 1,4-addition to conjugated dienes was the 1,4-cycloaddition reaction. There is a considerable variety of bis-heterodienophiles available and consequently the scope of the reaction is large<sup>4</sup>.

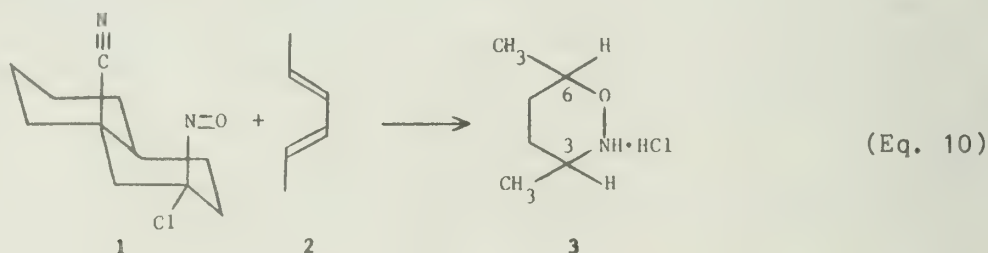




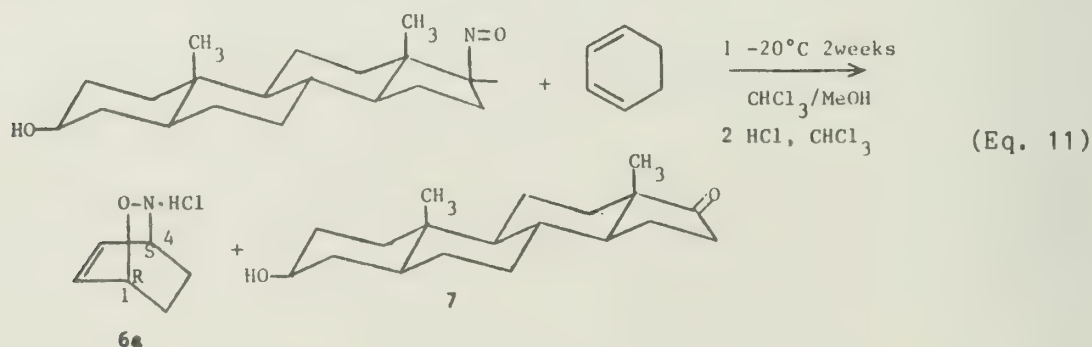
These reactions provide a large number of five- or six-membered heterocycles. These, after reductive cleavage, afford versatile intermediates for other synthetic transformations.

### Diastereoselective Diels-Alder Reaction

In 1976, Nitsch found<sup>20</sup> that reaction of chiral 2-chloro-2-nitroso-9-cyanodecalin **1** with trans, trans-2,4-hexadiene **2** gave adduct **3** in 83% yield (Eq. 10), after spontaneous cleavage from the decalin moiety. The optical purity was 39%, with the S-configuration at C-6 predominating.



An improvement in stereoselectivity was achieved by Sabuni<sup>21</sup> by using the steroid-derived compound **4** (Eq. 11). The optically active (1R,4S)-adduct **6a** was



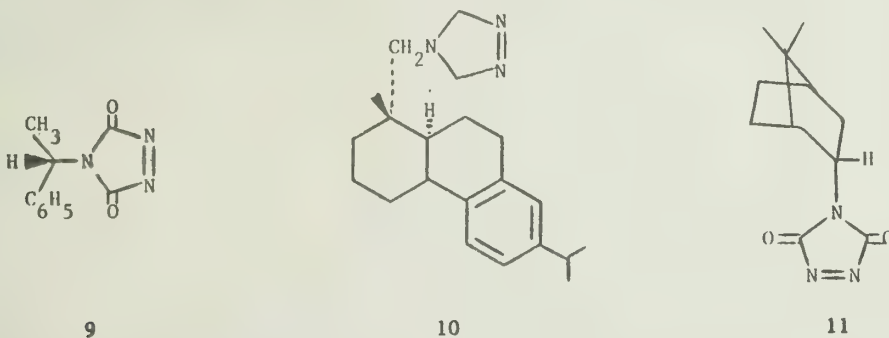
obtained in 69% yield (e.e.  $\geq 95\%$ ) with **7** (72% yield), the precursor of **4**, produced as a byproduct. In principle, the (1S,4R)-adduct **6b** could be obtained from the enantiomer of **4**, if this compound could be synthesized.

In 1984, Felber found<sup>22</sup> that reagent **8** is a suitable dienophile for the synthesis of (1*S*, 4*R*)-**6b** (see Eq. 12). This reaction proceeds in 65% yield (ee  $\geq$  95%).



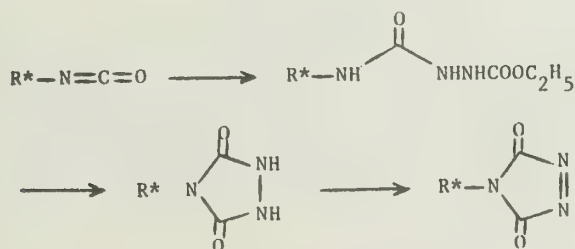
The high diastereoselectivity achieved in the above cases may result because free rotation around the C-NO bond is limited by the presence of a rigid molecular framework and bulky groups around the C-NO-moiety. The diene in its least hindered orientation then approaches from essentially one side of the nitroso group.

In 1980, kinetic resolution of racemic dienes **12** and **13** into their optically active forms was investigated by Paquette<sup>23</sup> using the optically pure triazolinediones **9**, **10** and **11**. These triazolinediones were prepared from (*S*)-

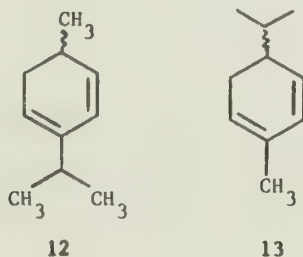


(-)- $\alpha$ -methylbenzylamine, dehydroabietylamine, and endo-bornylamine via the respective isocyanates and urazoles, (Scheme I).

#### Scheme I



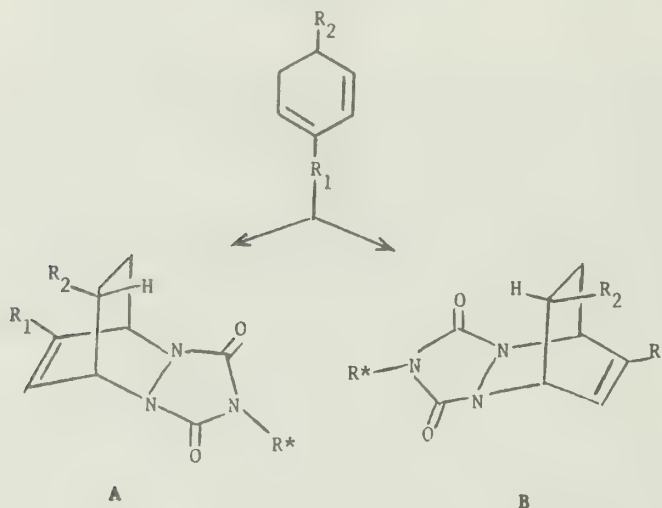
It was proposed that the Diels-Alder reaction of one of these triazolinediones with racemic **12** or **13** would form a pair of diastereomers (Scheme II) at different





rates and in dissimilar amounts due to differing transition state energies. However, only small differences in the rates of formation of **A** and **B** were observed. The asymmetric inductions ranged from 0-12%.

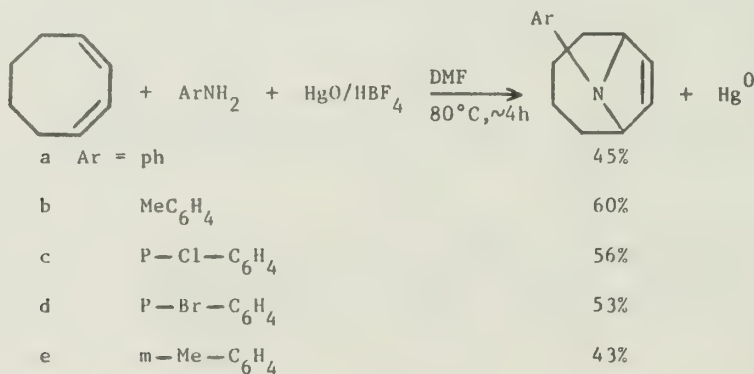
Scheme II



### Nucleophilic Addition

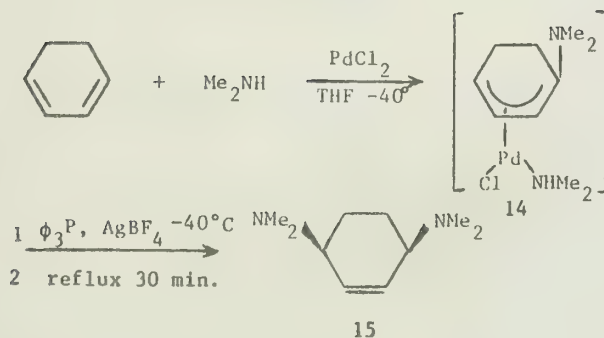
A simple method for the one-step amination of conjugated dienes was reported by Barluenga<sup>24</sup> in 1982. Reaction of 1,3-cyclooctadiene with primary aromatic amines, in the presence of mercury(II) oxide-tetra-fluoroboric acid, gave amination adducts (Scheme III) in moderate yield.

Scheme III



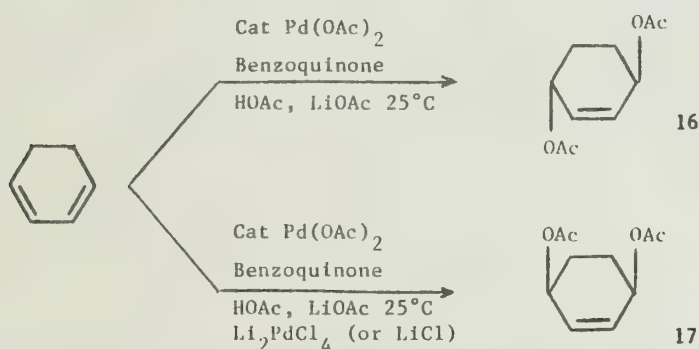
In 1979, Akermark<sup>25</sup> found that palladium-catalyzed amination of 1,3-cyclohexadiene with dimethyl amine, followed by addition of triphenylphosphine and  $AgBF_4$ , gave the bis-adduct **15** in 22% yield with  $> 94\%$  cis-configuration (Scheme IV).

Scheme IV



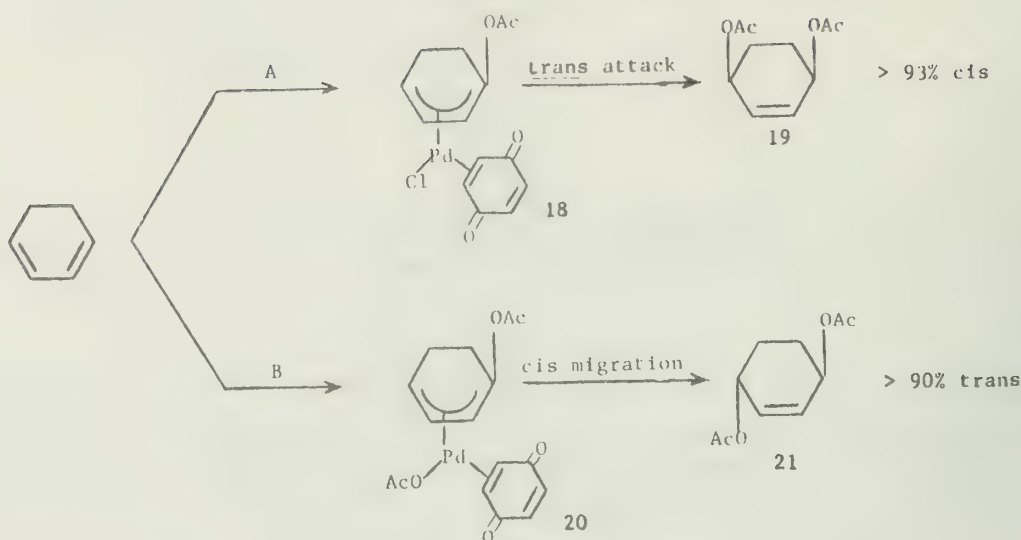
It was known early in 1971,<sup>26</sup> that the palladium-catalyzed reaction of acetic acid with 1,3-cyclohexadiene produces 1,4-diacetoxy-cyclohex-2-ene with undetermined stereochemistry. Further studies by Bäckvall and Nordberg<sup>27</sup> have shown that cis-17 and trans-16 can be selectively obtained by controlling the concentration of chloride ion (Scheme V).

Scheme V

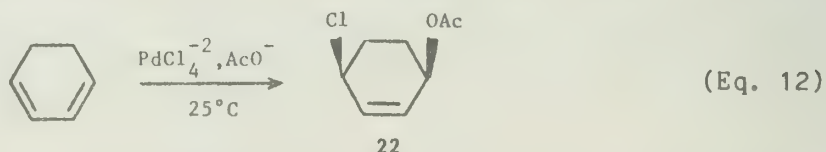


The stereochemical results can be interpreted by the mechanism shown in Scheme VI. In the presence of chloride ion (Scheme VI A) external trans-attack by acetate on the intermediate ( $\pi$ -allyl)-palladium complex 18 gives cis-19. In the chloride-free case, cis-migration of coordinated acetate from palladium to  $\text{C}_4$  gives trans-21.

Scheme VI



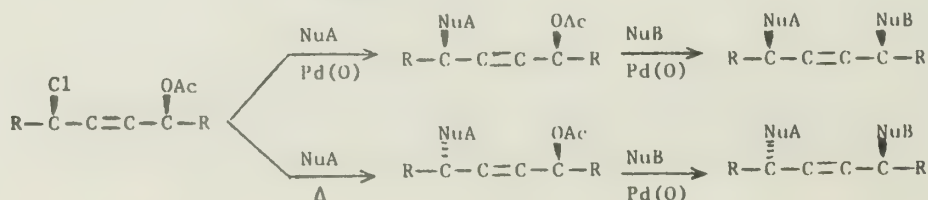
With unsubstituted cyclodienes (no. of carbon  $\leq 7$ ) this reduction gives exclusively 2,4-addition with high stereoselectivity. Except for butadiene, acyclic dienes also show a high selectivity for the formation of 1,4-isomers usually forming predominantly the E olefin.<sup>28</sup> Bäckvall<sup>29</sup> also found that increased concentration of chloride ion gave cis-1-acetoxy-4-chlorocyclohex-2-ene. 22. in 89% yield (> 98% cis) (Eq. 12). The proposed in this case (Eq. 12) is similar to that shown in Scheme



VIA. External attack on ( $\pi$ -allyl)-palladium intermediate by chloride ion gave 22. Unsubstituted cyclic dienes with 6 or 7 membered rings afforded products with >97% stereoselectivity and regioselectivity but the stereoselectivity of 1,4-addition acyclic dienes varies with the structure of the dienes.

An important aspect of the palladium-catalyzed 1,4-acetoxychlorination is that it provides useful intermediates for organic synthesis. The chloro and acetoxy groups in the product can be sequentially substituted stereoselectively<sup>30</sup> as shown in Scheme VII.

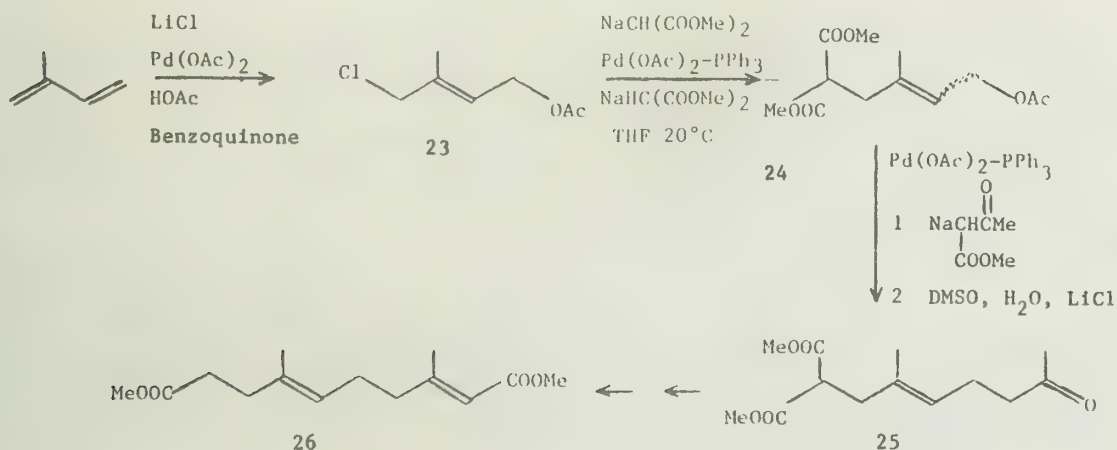
Scheme VII





This process has been used in the synthesis of the monarch butterfly pheromone<sup>1d</sup> 26 (Scheme VIII).

Scheme VIII



In conclusion, the regio- and stereocontrolled 1,4-addition to conjugated dienes can be achieved by the Diels-Alder reaction or the palladium-catalyzed nucleophilic addition. The two reactions provide access to a wide range of useful synthons for organic transformations. In addition, the Diels-Alder reaction in some cases gives products of reasonable enantiomeric excess.

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# THE EXCITED STATE CHEMISTRY OF SHORT-LIVED INTERMEDIATES

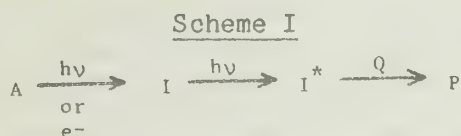
Reported by Daniel E. Falvey

October 10, 1985

## Introduction

The introduction of high-power, pulsed lasers has made it possible to examine the reactivities of short-lived species such as free radicals, carbenes, radical ions, diradicals, and nitrenes.<sup>1</sup> These intermediates play a central role in the understanding of organic reaction mechanisms. In a conventional flash-photolysis experiment, usually only the ground state or thermal reactions of these species are monitored; the excited-state or photochemistry of reactive intermediates has been largely neglected.

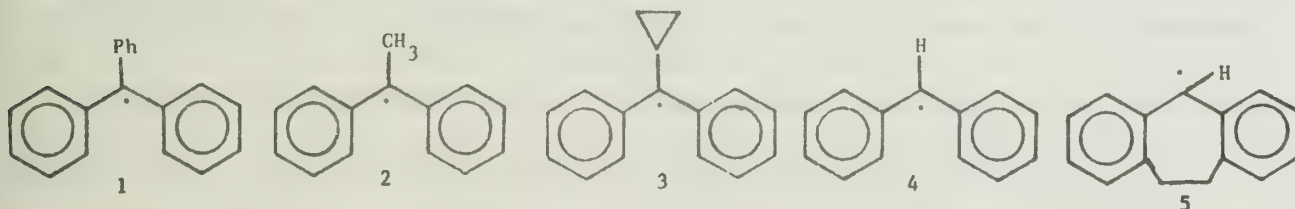
Recently, several reports have appeared in the literature where the photochemistry of reactive intermediates has been explored, largely through time-resolved laser techniques. A general reaction scheme for this sort of experiment is shown in Scheme I. The reactive intermediate, I, is generated by



photolysis of a suitable precursor, A. This is called the "synthesis" step. In the "excitation" step the intermediate is excited by a second photon. Usually this experiment is done with two pulsed lasers. In some cases the synthesis step is accomplished by pulse radiolysis. In special cases, it is possible to carry out both synthesis and excitation with a single, powerful laser pulse. The progress of the subsequent reactions can be monitored using either transient absorption or by monitoring the fluorescence lifetime of I\*, the excited state of the intermediate.

## Arylmethyl Radicals

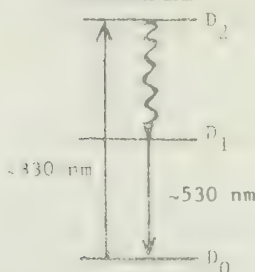
Although extensive theoretical and experimental work has been done on the photophysics of arylmethyl radicals over the past 25 years,<sup>2</sup> only recently has the photochemistry of these species been explored. A general energy-level diagram for



these systems is shown in Scheme II. The lowest excited state, D<sub>1</sub>, is relatively long-lived (200-1500 ns). The strongest absorption band is the D<sub>0</sub>→D<sub>2</sub> transition in the ultraviolet region.



Scheme II



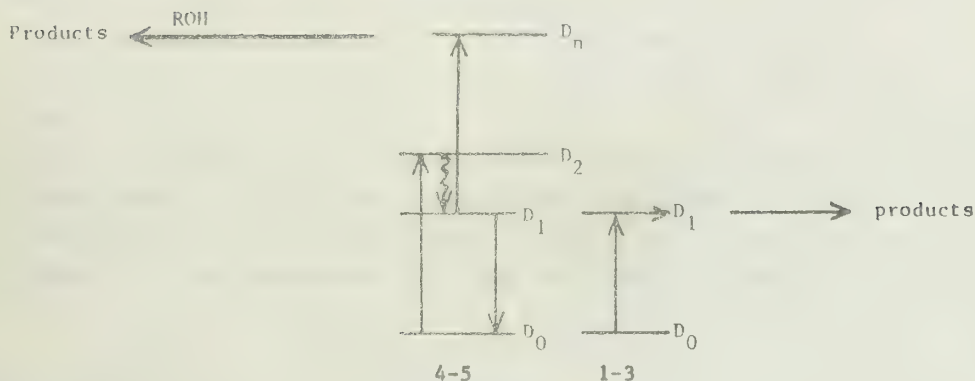
A series of diphenylmethyl radicals (1-5) was examined to discern the relationship of structure to the reactivity of these species.<sup>3</sup> These radicals were prepared by pulse radiolysis of the corresponding carbinols or chlorides, then photolysed with the second harmonic (347 nm) of a Q-switched ruby laser. When radical 1 was excited, a new absorption band at 490 nm appeared immediately after the laser pulse. Bleaching (negative absorption change) due to depletion of the ground state radical was recorded at 338 nm. Both the bleaching and the absorption were "permanent" on the time scale of the experiment (ca. 200  $\mu$ s). The quantum yield for bleaching was calculated to be  $1.05 \pm 0.01$ . These results showed no solvent effect and the change in absorption was shown to be linear with the concentration of 1. Radicals 2 and 3 showed parallel behavior. No fluorescence could be detected from any of the radicals 1-3. From these data it was concluded that 1-3 reacted from the first excited state,  $D_1$ , by a unimolecular, one-photon process which was suggested to be a cyclization shown in Scheme III.

Scheme III



In contrast, both 4 and 5 showed intense fluorescence from their  $D_1$  states with lifetimes 278 and 263 ns respectively. In alcohols and water, 4 showed 40-55% "permanent" bleaching, while in acetonitrile, the excited radical returned almost quantitatively back to its ground state. Both the fluorescence lifetime and quantum yield were invariant in all of the solvents examined. Similarly, 5 showed strongly solvent-dependent bleaching yet its fluorescence lifetime and fluorescence quantum yield were unaffected by variations in the solvent. In the case of 4 and 5, it was concluded that the processes responsible for "permanent" bleaching did not occur from  $D_1$ . In all cases, these radicals were believed to react via a biphotonic process from some higher excited state,  $D_n$ . These results are summarized in Scheme IV. The dichotomy of reactivity between the groups of 1-3 and 4-5 was explained

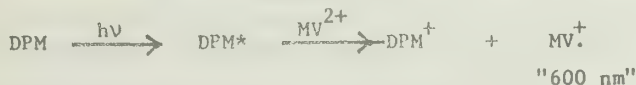
Scheme IV



by the difference in the degree of twist of the phenyl groups between the two sets of radicals.

The excited-state reactions of diphenylmethyl radical (DPM) with a variety of substrates was measured using a two-laser nanosecond flash photolysis apparatus.<sup>4</sup> To investigate its excited-state reactivity toward single-electron transfer, DPM was irradiated in the presence of an electron acceptor, methyl viologen ( $MV^{2+}$ ). The rate of reaction for the excited state of DPM ( $DPM^*$ ) with  $MV^{2+}$  was found to be  $1.30 \times 10^{10} \text{ M}^{-1}\text{s}^{-1}$ . An absorption at 600 nm attributed to  $MV^{+ \cdot}$  was also detected suggesting that  $DPM^*$  reacted with  $MV^{2+}$  by electron transfer to yield solvent-separated ion pairs (Scheme V). The reaction of  $DPM^*$  with an electron donor, triethylamine was found to proceed with a rate constant of  $5.2 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ .

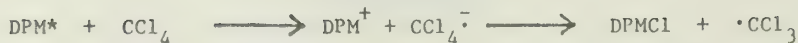
Scheme V



The reactions of  $DPM^*$  toward the H-atom donors, 1,4-cyclohexadiene and tri-n-butyltin hydride was investigated to determine if the extra potential energy afforded the excited state would lead to enhanced reactivity toward these substrates.<sup>5</sup>  $DPM^*$  was found to live 60 ns in neat 1,4-cyclohexadiene and 170 ns in neat tri-n-butyltin hydride. In benzene, a solvent which is inert toward  $DPM^*$ , the lifetime for  $DPM^*$  was 255 ns. Thus, it was concluded that the reactivity of excited state free radicals toward H-atom donors is not greatly enhanced over the ground state.

Oxygen was found to react with  $DPM^*$  with a rate constant of  $8.7 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ , suggesting that the primary mechanism is energy transfer to form singlet oxygen. In methanol,  $CCl_4$  quenched  $DPM^*$  with rate constant of  $1.6 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ . Diphenylmethyl chloride was isolated from reaction mixtures where DPM was subject to two-photon irradiation in neat  $CCl_4$ . Thus, it was suggested that the reaction involves electron transfer followed by transfer of chloride ion to DPM (Scheme VI).

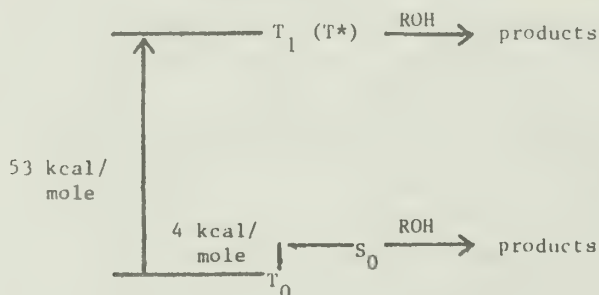
Scheme VI



### Diarylcarbenes

The thermal chemistry of diarylcarbenes has been exhaustively explored and documented.<sup>6</sup> The two lowest electronic states of diaryl carbenes are of different spin multiplicities, one is a triplet,  $T_0$ , and the other is a singlet,  $S_0$ . The triplet-triplet fluorescence spectrum has been measured and characterized both in rigid glass matrix and in solution.<sup>7</sup>

Scheme VII



The reaction rates of the excited triplet state of diphenylcarbene ( $T^*$ ) with various alcohols was measured using picosecond fluorescence techniques.<sup>7,8</sup> The ground state of the carbene was generated from diazodiphenylmethane by a 20 ps pulse followed by a second pulse from the same laser which then promoted the carbene to its excited triplet state. It was found that fluorescence from  $T^*$  was rapidly quenched by alcohols. The kinetic isotope effect was calculated by substituting deuteriums for the hydroxyl protons. The  $k_H/k_D$  was found to range from 1.5 to 1.6 for each of the alcohols studied. Finally, it was noted that the relative reactivities of the alcohols toward  $T^*$  followed the same order as their reactivities toward the lowest singlet state,  $S_0$ . These results were taken to show that  $T^*$  reacted with alcohols by direct insertion into the O-H bond of the alcohol.

Ground-state triplet carbenes are known to be highly reactive toward olefins. Diphenylcarbene was photolysed in the presence of isoprene, using the same apparatus described for the alcohol reactions studies.<sup>9</sup> The ground state of diphenylcarbene reacts with isoprene with a rate constant of  $3.5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ . The corresponding rate constant for the reaction of  $T^*$  with isoprene is  $2.1 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ .

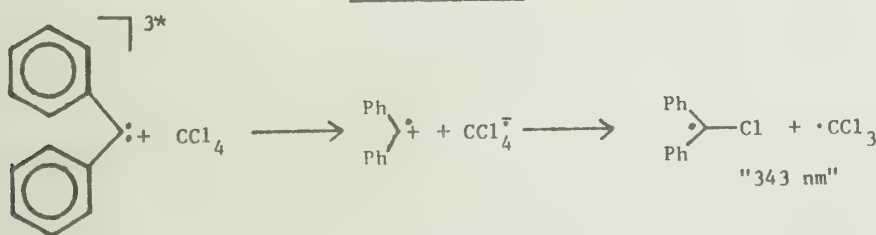
The reaction of  $T^*$  with amines was investigated. These reactions were studied both by the picosecond fluorescence method outlined above,<sup>9</sup> as well as by nanosecond transient absorption.<sup>10</sup> In the nanosecond experiments, both the synthesis and the excitation were accomplished by a single laser pulse. Both experiments showed that  $T^*$  was quenched by tertiary amines as well as primary and secondary amines. A plot of the log of the bimolecular rate constant for this reaction versus the oxidation



potential of the amines is linear with a negative slope. Thus, it was concluded that quenching mechanism involved single electron transfer in the primary step.

The reaction of the excited triplet of di(p-toyl)carbene with carbon tetrachloride in isooctane solvent was measured using nanosecond transient absorption.<sup>11</sup> It was found to react with rate constant of  $1.1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ . The quenching of the excited carbene did not yield ground state carbene. In fact a new absorption attributed to the diphenylchloromethyl radical appeared at 343 nm. The mechanism advanced to explain these results was electron transfer from the carbene to carbon tetrachloride followed by chloride ion transfer (Scheme VIII).

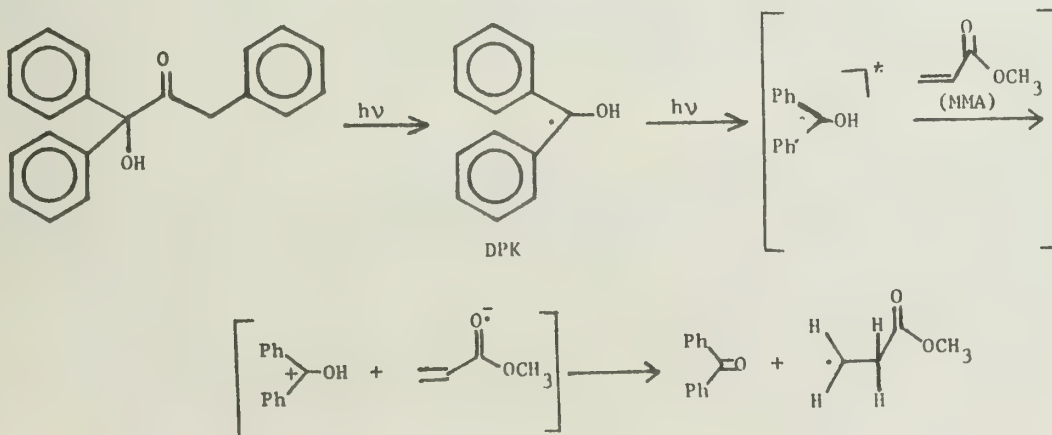
Scheme VIII



## Ketyl Radicals

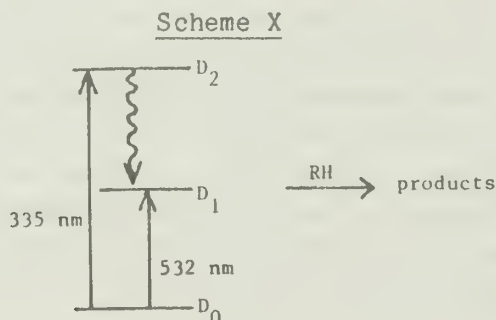
The diphenylketyl radical (DPK) has a strong absorption in the visible region ( $\lambda_{\text{max}} = 540 \text{ nm}$ ),<sup>12</sup> making it a very convenient and attractive system for study by flash-photolysis. There has been considerable interest in the use of DPK in initiator systems for photopolymerization.<sup>13</sup> DPK was generated by the Norrish type I cleavage of  $\alpha$ -phenylbenzoin and then excited by the same laser pulse.<sup>14,15</sup> The rates of reaction for the excited radical, DPK\*, with methyl methacrylate (MMA) and various onium salts was determined by measuring the fluorescence lifetime of DPK\*. The rate constant for the reaction of DPK\* with MMA was 300,000 times larger than DPK. The mechanism shown in Scheme IX is offered to account for this behavior.

Scheme IX



The fluorescence from DPK\* is also quenched by various onium salts.<sup>16</sup> Where electron transfer is thermodynamically favorable from the ground state, DPK\* does not react appreciably faster than DPK. When the reduction potentials of the onium salts were such that electron transfer was thermodynamically disfavored from the ground state, DPK\* reacted up to  $10^3$  times faster than the ground state. This suggested that the primary quenching mechanism by both onium salts and olefins was electron transfer.

The reactions of DPK\* with H-atom donating solvents was measured using time-resolved transient absorption with a two-laser apparatus.<sup>17</sup> DPK was generated by photolysis of benzophenone with an excimer laser and the excitation step was accomplished with either the second or third harmonic of a Nd:YAG laser. The rate constants for the reaction of DPK\* with isopropanol and cyclohexane in acetonitrile were  $7 \times 10^8$  and  $4 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ , respectively. Upon reaction with either substrate, bleaching (a negative change in absorption) at 532 nm due to depletion of the ground state radical was observed. This bleaching was "permanent" on the 2  $\mu\text{s}$  timescale of the experiment. These results were found to be independent of the excitation wavelength. From these data it was inferred that DPK\* reacted with isopropanol and cyclohexane by H-atom abstraction. Furthermore, this reaction occurred from the lowest excited state of DPK,  $D_1$  (Scheme X).

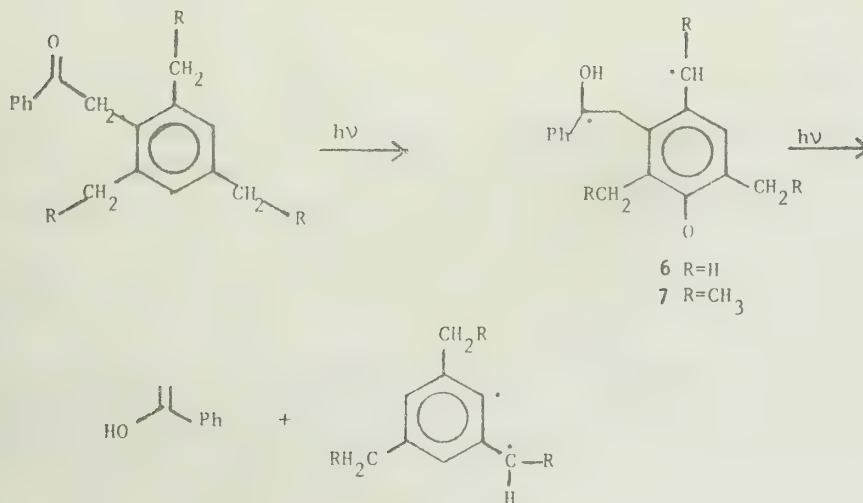


Permanent bleaching was observed for DPK in the presence of water and in neat acetonitrile. It was believed that heterolysis of the O-H bond of the ketyl radical in polar solvents accounted for this permanent bleaching.

### 1,5 and 1,3 Diradicals

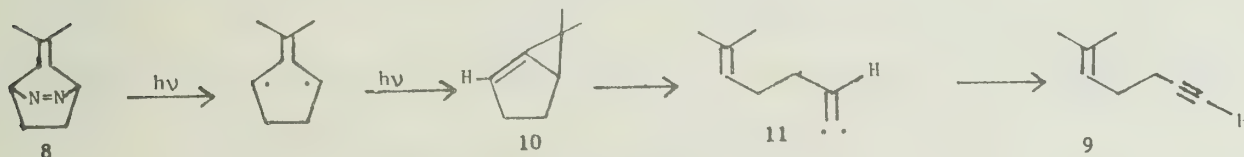
Only a few, preliminary reports on the excited state reactions of diradicals have appeared.<sup>19,20</sup> In each case it was shown that diradicals will undergo novel rearrangements and fragmentations not possible from their ground state. The 1,5 diradicals, **6** and **7** were formed from the Norrish type II reactions of their corresponding ketones.<sup>19</sup> These radicals were then excited with an excimer laser. Products resulting from the cleavage of the diradicals shown in Scheme XI were detected both by transient absorption as well as by GC analysis of the product mixture.

Scheme XI



The 1,3 diradical, 2-isopropylidenecyclopentane-1,3-diyl, also rearranged to yield products different from those obtained from thermal reactions. The diradical was prepared in a rigid matrix by irradiation of the diazene, **8**.<sup>20</sup> Subsequent irradiation of the diradical produced the eneyne, **10** which constituted 93% of the monomeric products. Upon thermolysis, **8** yields a very complex mixture of which **9** is found in 1% yield. A mechanism was proposed involving the vinylidene carbene, **11** which upon hydrogen shift yields the eneyne, **9** (Scheme XII).

Scheme XII



**Summary**

The excited states of reactive intermediates show, in many cases, much different reactivity than their corresponding ground states. The most general characteristic of reactive intermediate photochemistry is the enhanced ability to undergo single-electron transfer as observed for diarylmethyl radicals, ketyl radicals, and carbenes. Diradicals, and in some cases arylmethyl radicals, undergo novel rearrangements in their excited states which are not possible from the ground state.



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# RECENT PROGRESS IN KETONE AND ESTER $\alpha$ -OXYGENATION

Reported by Wei Jane Liao

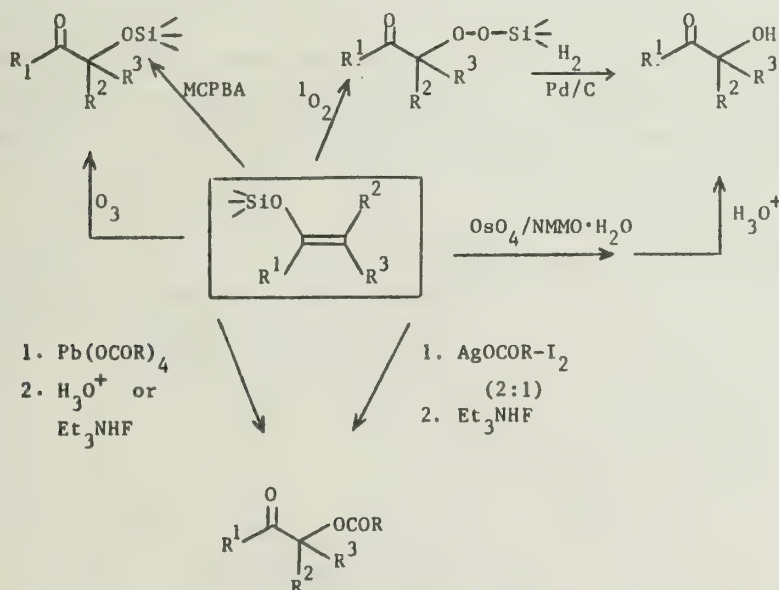
October 17, 1985

$\alpha$ -Oxygenated carbonyl compounds are important synthetic intermediates (e.g. acorenone-B<sup>1</sup> and the prostaglandin analogues<sup>2</sup>), and also occur naturally in many forms (e.g. daunomycinone<sup>3</sup> and cortisone<sup>4</sup>). Thus, the synthetic problem of  $\alpha$ -oxygenation of carbonyl compounds continues to be the subject of numerous studies. The preparation of  $\alpha$ -hydroxy ketones from substrates other than ketones (except the hydrolysis of  $\alpha$ -halo ketones) has been reviewed by McElvain.<sup>5</sup> This report will discuss the different synthetic approaches which have been used to introduce the oxygen functionality adjacent to the carbonyl group of ketones and esters directly from their derivatives (e.g. enol silanes, enolates).

## 1. Ketones

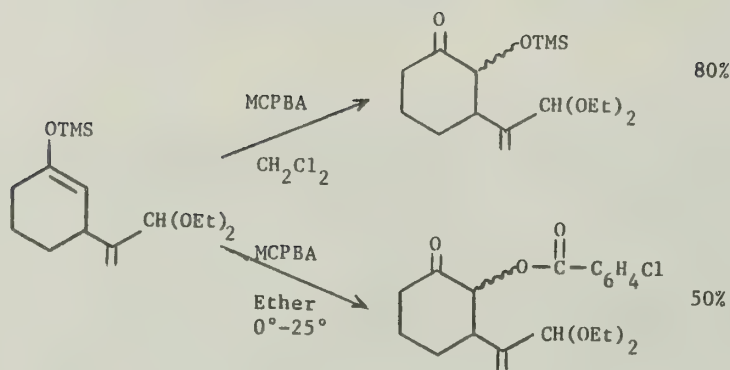
$\alpha$ -Oxygenation via Enol Silanes. Enol silanes are widely employed in oxygenation due to their ready availability<sup>6</sup> (Scheme I). The oxidation is

Scheme I

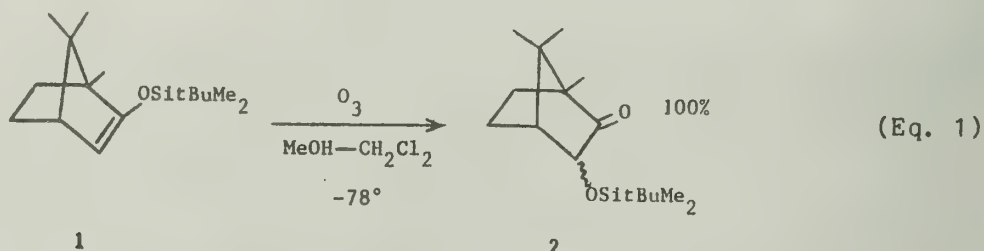


regiospecific relying on the double bond placement in the enol silanes. *m*-Chloroperbenzoic acid (MCPBA) oxidation of enol silanes<sup>7</sup> in methylene chloride or hexane yields  $\alpha$ -siloxy ketones which, on treatment with acid or base, afford  $\alpha$ -hydroxy ketones in high yields. When ether is used as solvent, a competitive attack by *m*-chlorobenzoic acid on the epoxy siloxy intermediate is favored, resulting in the formation of  $\alpha$ -benzoyloxy ketones<sup>7d</sup> (Scheme II).

Scheme II

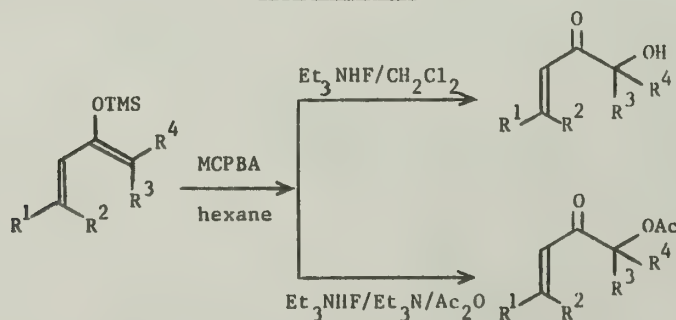


A related reaction has been reported by Heathcock<sup>8</sup> (Eq. 1). Treatment of enol silane **1** with ozone resulted in the formation of  $\alpha$ -siloxy ketone **2** instead of the expected olefin cleavage product.

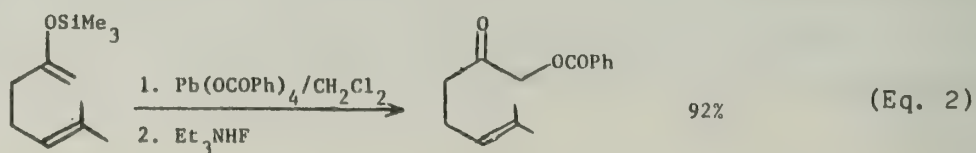


In  $\alpha,\beta$ -unsaturated ketones,  $\alpha$ -oxygenation is achieved by MCPBA oxidation of 2-trimethylsiloxydienes, followed by hydrolysis or acetylation to afford the corresponding  $\alpha$ -hydroxy or  $\alpha$ -acetoxy enones (Scheme III).<sup>9</sup> The oxidation occurs regiospecifically at the  $\alpha'$ -carbon in high yield.

Scheme III

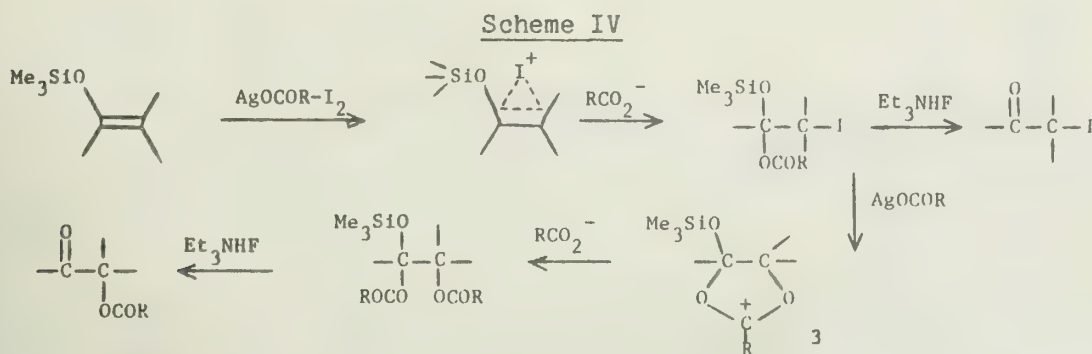


Trimethylsilyl enol ethers are oxidized by lead tetrabenzoate (LTB)<sup>10</sup> or lead tetraacetate (LTA)<sup>11</sup> in methylene chloride or benzene at room temperature to yield, after hydrolysis, the corresponding  $\alpha$ -carboxy ketones in high yields. Remote olefinic functionality remains intact under the mild reaction conditions (Eq. 2).

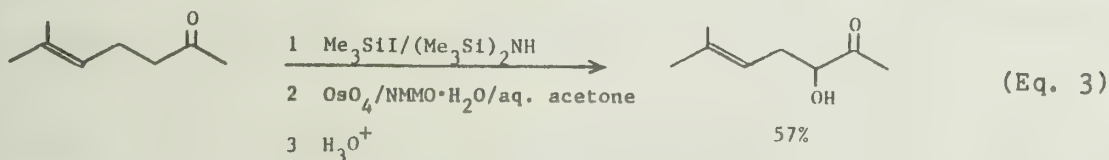




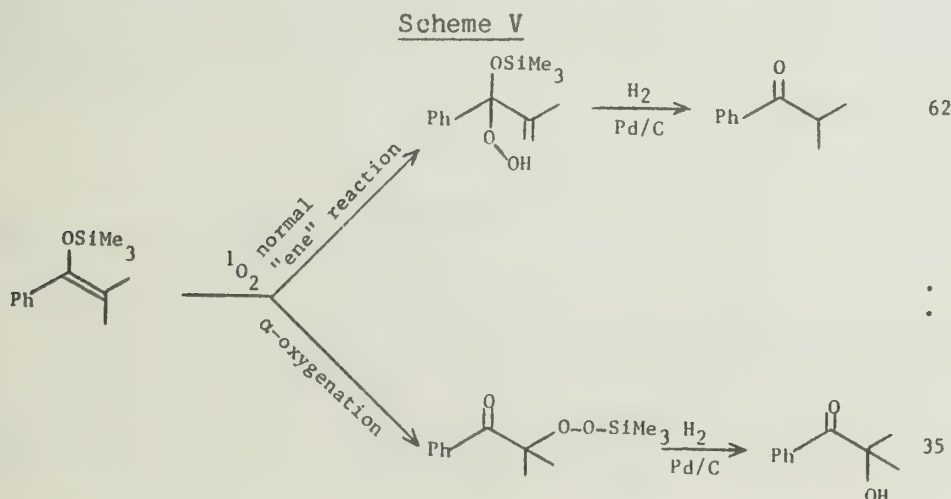
In a series of reactions of cyclic enol silanes with silver carboxylate-iodine (2:1), Rubottom<sup>12</sup> showed that the oxidation proceeded successfully with five- and six-membered-ring enol silanes through the proposed cyclic intermediate **3**, Scheme IV. In larger ring sizes where the formation of **3** is disfavored,  $\alpha$ -iodo ketones became important side products.



McCormick and co-workers<sup>13</sup> employed a catalytic amount of osmium tetroxide together with one equivalent of N-methylmorpholine-N-oxide monohydrate (NMMO·H<sub>2</sub>O) in the oxidation of trimethylsilyl enol ethers. Subsequent workup afforded  $\alpha$ -ketols in 60-95% yields (Eq. 3). Generally,  $\alpha$ -hydroxylation at methine or methylene carbons proceeds better than at methyl carbons.

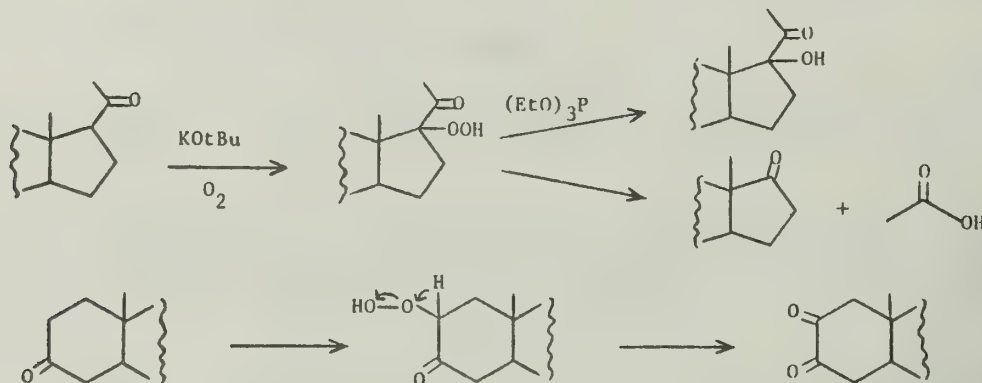


$\alpha$ -Hydroxylation can also be carried out photochemically.<sup>14</sup> In substrates having allylic hydrogens available to undergo a normal "ene" reaction, however, the  $\alpha$ -oxygenation will be suppressed (Scheme V).<sup>14b</sup>



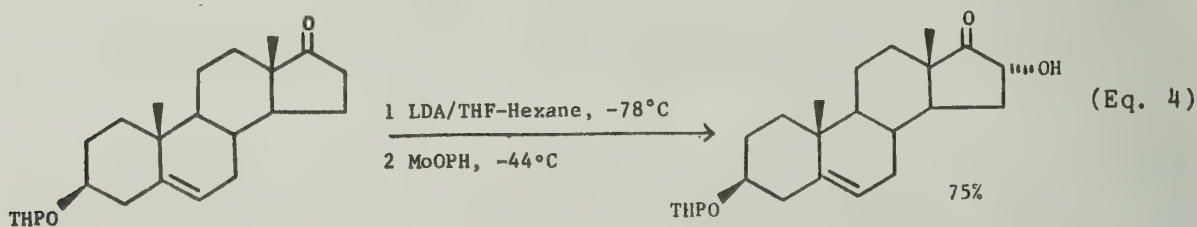
$\alpha$ -Oxygenation via Enolates.  $\alpha$ -Hydroxylation of ketones is commonly accomplished by base catalyzed oxygenation<sup>15</sup> together with the in-situ triethyl phosphite reduction of labile hydroperoxide intermediates<sup>16</sup> (a modification used to minimize the oxidative  $\alpha$ -carbon cleavage<sup>15a,17</sup> (Scheme VI)). In systems bearing an

Scheme VI

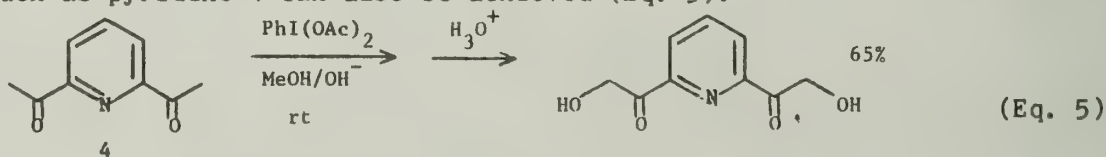


enolizable methyl or methylene group, hydroperoxide fragmentation to an  $\alpha$ -dicarbonyl compound is a serious side reaction.<sup>15a,17b,18</sup>

The direct oxygenation of lithium enolates with the molybdenum peroxide reagent  $\text{MoO}_5 \cdot \text{pyridine} \cdot \text{HMPA} (\text{MoOPH})$  provides a promising method for the hydroxylation at  $\alpha$ -methine or  $\alpha$ -methylene positions<sup>19</sup> (Eq. 4). Methyl ketones and enones, however, gave less satisfactory results.



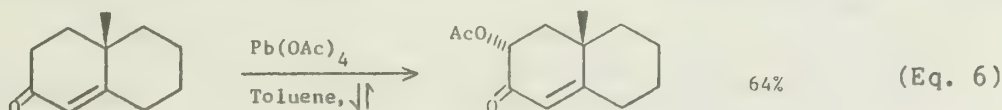
The use of hypervalent compounds, i.e. iodosobenzene, o-iodosylbenzoic acid and diacetoxyphenyliodine (III) as oxygen transfer reagents in the  $\alpha$ -hydroxylation of carbonyl compounds has been investigated recently.<sup>20</sup> Moderate to high yields of the resulting acyloins were obtained. The oxygenation of methyl ketones and symmetrical systems such as pyridine **4** can also be achieved (Eq. 5).



Direct  $\alpha$ -Acetoxylation of Ketones. Lead tetraacetate (LTA), mercuric acetate and thallium triacetate have been used for  $\alpha$ -acetoxylation of ketones.<sup>21</sup>  $\alpha$ -Acetoxylation of enolizable ketones by LTA in hot benzene or acetic acid proceeds in moderate yield. In addition to mono-acetoxylation, however,  $\alpha, \alpha'$ -diacetoxylation<sup>22</sup> and rearrangement products<sup>23</sup> may be found.

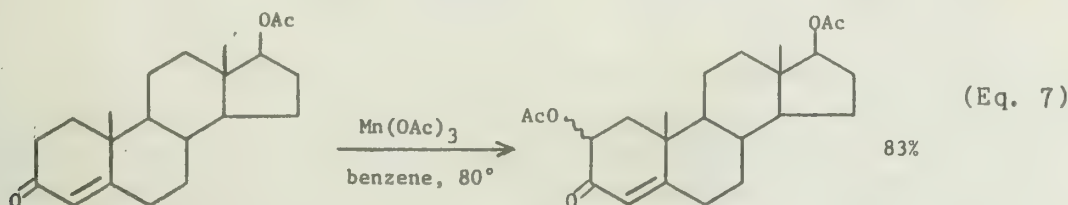
$\alpha$ -Acetoxylation of ketones by mercuric acetate proceeds at higher temperature (130-200°C) in moderate yield. This method occasionally failed due to unreactivity, side reactions<sup>24</sup> or poor regioselectivity.<sup>25</sup>

LTA acetoxylation of enones mostly occurs at the  $\alpha'$ -carbon<sup>21,26</sup> (Eq. 6). In



certain  $\alpha, \beta$ -unsaturated ketones such as pulegone,  $\alpha$ -acetoxylation is the major pathway,<sup>27</sup> while with mercuric acetate  $\alpha'$ -acetoxylation predominates.<sup>28</sup>

Recently, Watt<sup>29</sup> showed that  $\alpha'$ -acetoxylation of enones can be accomplished in high yields by manganese triacetate (Eq. 7).



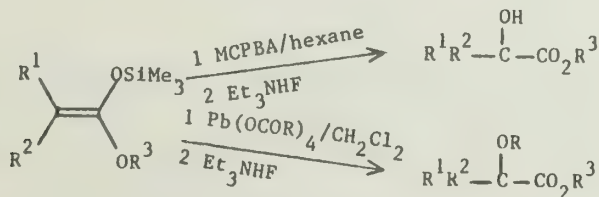
Miscellaneous Methods.  $\alpha$ -Oxygenation of ketones has been carried out via enol acetate photochemically in the presence of LTA<sup>30</sup> and also by anodic<sup>31</sup> or peracid<sup>32</sup> oxidation. Highly branched  $\alpha$ -acetoxy ketones can be obtained by electrochemical reduction of  $\alpha, \alpha'$ -dibromo ketones in acetic acid.<sup>33</sup> Benzeneseleninic anhydride oxidation of ketones has also been investigated.<sup>34</sup>

## 2. Esters

The methodology developed for the preparation of  $\alpha$ -oxygenated esters is similar to that of  $\alpha$ -oxygenated ketones. LTA is rarely employed due to the low concentration of the reactive enol tautomer under the conditions normally used for LTA oxidation.

$\alpha$ -Oxygenation via Alkyl Trimethylsilyl Ketene Acetals.<sup>35</sup> Oxidation of trimethylsilyl ketene acetals can be achieved by MCPBA in hexane<sup>36</sup> or lead (IV) carboxylate in methylene chloride<sup>37</sup> (Scheme VII). The choice of

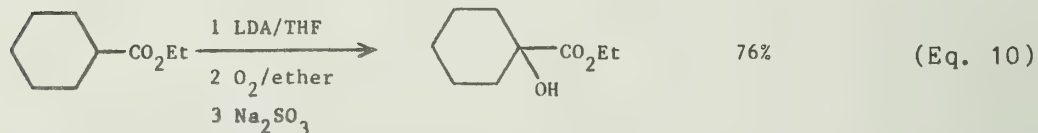
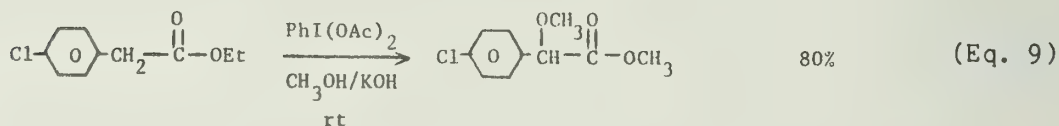
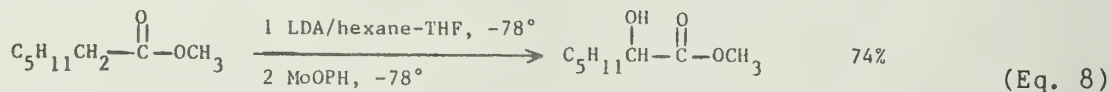
Scheme VII



solvent is crucial for the success of oxidation in both cases. Both methods give comparably high yields.<sup>36,37</sup>



$\alpha$ -Oxygenation via Ester Enolates. MoOPH<sup>19</sup> reagent, diacetoxyphenyliodine (III)<sup>38</sup> or molecular oxygen<sup>39</sup> can be employed for  $\alpha$ -oxygenation of esters (Eq. 8, 9, 10). For the oxygenation of enolates of unbranched esters, MoOPH and diacetoxyphenyliodine (III) are suggested due to reactions such as  $\alpha$ -carbon cleavage in molecular oxygen oxidation.<sup>39</sup>



Asymmetric  $\alpha$ -Hydroxylation of Enolates. Asymmetric  $\alpha$ -oxygenation of enolates has not been widely investigated until recently. As in diastereoselective alkylation, chiral auxiliaries have been utilized. Tamm and co-workers<sup>40</sup> have demonstrated that the  $\alpha$ -hydroxylation of camphor-derived ester enolates with MoOPH reagent displays a moderate diastereoselectivity. On the other hand, Evans<sup>41a</sup> achieved a high diastereoselection in 2-(phenylsulfonyl)-3-phenyl-oxaziridine (**9**)<sup>41b</sup> oxidation of chiral imide enolates, **10** and **11**, (Scheme VIII). The results are summarized in Table I.

Scheme VIII

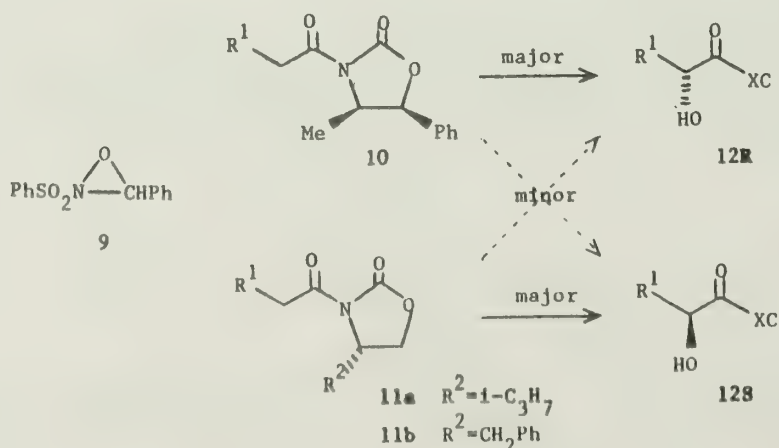
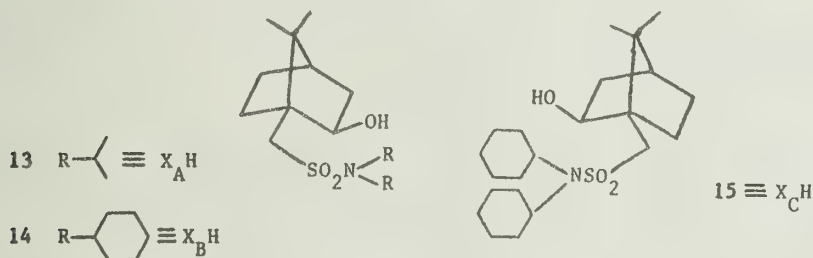


Table I

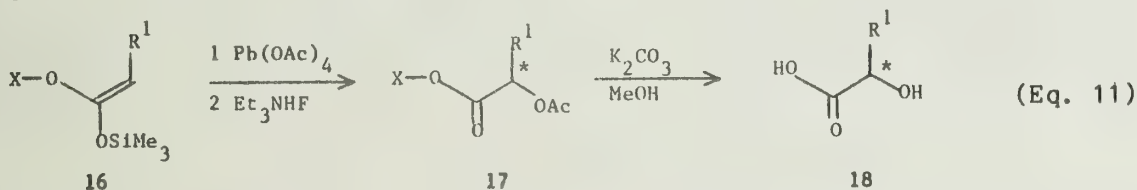
imide	ratio 12R:12S	isolated yield, %
10 ( $R^1 = \text{Ph}$ )	90:10	77 (R)
10 ( $R^1 = \text{Et}$ )	94:6	86 (R)
10 ( $R^1 = \text{CH}_2\text{CH}=\text{CH}_2$ )	95:5	91 (R)
10 ( $R^1 = t\text{-C}_4\text{H}_9$ )	99:1	94 (R)
10 ( $R^1 = \text{CH}_2\text{Ph}$ )	94:6	86 (R)
11a ( $R^1 = \text{CH}_2\text{Ph}$ )	5:95	85 (S)
11b ( $R^1 = \text{CH}_2\text{Ph}$ )	5:95	83 (S)
11a ( $R^1 = i\text{-C}_3\text{H}_7$ )	1:99	86 (S)

Methanolysis of the resulting  $\alpha$ -hydroxy carboximides affords the corresponding  $\alpha$ -hydroxy methyl esters in 80-90% yield without racemization.

The use of chiral sulfonamide **13-15** in the asymmetric  $\alpha$ -acetoxylation



of carboxylic esters has been reported by Oppolzer<sup>42</sup> (Eq. 11).



$\alpha$ -Acetoxyesters **17** were obtained in high diastereoselectivity upon treatment of ketene acetals **16** with LTA and  $\text{Et}_3\text{NHF}$  (Table II). Saponification of **17** gave hydroxy acids **18** in high enantiomeric purity.

Table II

Auxiliary X	$R^1$	d.e. (%) 17 (crude)	Yield (%) 17 (cryst.)	d.e. (%) 17 (cryst.)	Configuration 18
$\text{X}_A$	$\text{CH}_3$	88	60	100	R
$\text{X}_B$	$\text{C}_4\text{H}_9$	90.5	55	95	R
$\text{X}_C$	$\text{C}_8\text{H}_{17}$	96	67	98.6	S

## Summary

The  $\alpha$ -oxygenation of enolates and their silylated derivatives as well as other analogues has been studied extensively. MCPBA, lead (IV) carboxylates, MoOPH and KOtBu/O<sub>2</sub> are the reagents generally employed. In the field of asymmetric oxygenation, high diastereoselectivity has been achieved, while its scope still remains to be investigated further.

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## TOXINS OF THE BLUE-GREEN ALGAE: ACTIONS, STRUCTURES AND SYNTHESSES

Reported by Keith C. Bible

October 28, 1985

### Introduction

Algal toxins are a diverse and interesting group of compounds having profound effects upon mammalian neurologic, dermatologic and gastrointestinal structures. The toxicity of algal natural products was first suspected in 1878,<sup>1</sup> and it has been of concern to public health officials and livestock farmers throughout the intervening century. Toxins of blue-green algae (cyanophytes) are of particular interest and importance, for they account for a large portion of the human and animal toxicity attributable to algal toxins.<sup>2</sup>

Broadly speaking, blue-green algae can be divided into two major groups of organisms: marine and freshwater. Marine algal toxins have been responsible for many massive fish and shellfish kills, and have also resulted in animal and human deaths from the ingestion of toxin-contaminated seafood.<sup>2</sup> Freshwater algal toxins are of special concern, because they have been known to contaminate water supplies, resulting in large livestock and poultry kills (as well as human toxicity).<sup>2</sup> Further, treatment of water supplies by filtration through activated charcoal is necessary to remove these freshwater algal toxins, and other conventional water purification procedures do not remove or deactivate some freshwater toxins.<sup>3</sup>

Despite the extreme toxicity of many algal natural products, algal toxins may prove to be of value in clinical medicine. Many algal toxins have properties similar to useful anesthetic agents, and saxitoxin has been shown to be useful in inducing local anesthesia.<sup>4</sup> Several algal toxins also have antimicrobial, antifungal and antineoplastic activity, and the study and optimization of their biological activities (coupled with a minimization of their toxicities) may result in the production of useful chemotherapeutic agents.<sup>5</sup>

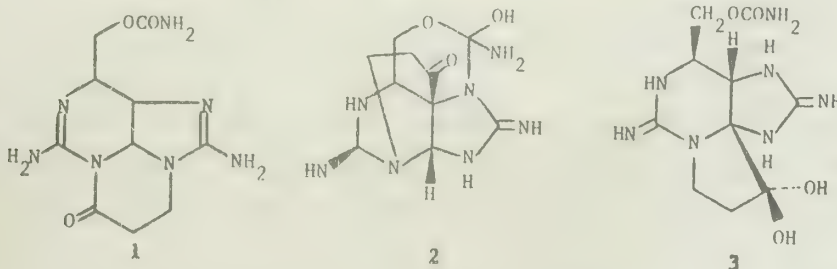
### Marine Algal Toxins

#### SAXITOXIN

Saxitoxin, commonly referred to as paralytic shellfish poison,<sup>6</sup> is the best studied marine blue-green algal toxin. Saxitoxin has been isolated from Gonyaulax catenella, Gonyaulax tamarens, Gonyaulax giganteus and Aphanizomenon flos-aquae<sup>7</sup> as well as from marine mussels,<sup>6</sup> clams<sup>6</sup> and scallops.<sup>8</sup> It is generally believed that the presence of saxitoxin in bivalves and scallops results from their ingestion of Gonyaulax algae rather than from independent production of the toxin.<sup>8</sup> It should be noted that saxitoxin is produced by both fresh-water (Aphanizomenon, a blue-green alga) and marine (Gonyaulax, dinoflagellates) algae. However, because this toxin was

first isolated from marine sources, it is generally classified as a marine algal toxin. Saxitoxin is among the most toxic substances known ( $LD_{50}=5-10 \mu\text{g/kg}$ , mice, IP),<sup>9</sup> and is potentially lethal to most fish and shellfish varieties. The  $LD_{50}$  for humans has been estimated to be about 1.0mg.

The earliest structural elucidation studies performed on saxitoxin were accomplished by Rapoport, et al.<sup>10</sup> in 1964 - resulting in 1 as a proposed structure. In 1971, Wong et al.<sup>11</sup> reported a revised structure 2, but both of these early structures turned out to be incorrect based upon two more recent, independent X-ray crystallographic studies.<sup>9,12</sup> These two, later studies not only established the structural formula of saxitoxin 3, but also established its stereochemistry.



The first (and only) total synthesis yet reported for saxitoxin was accomplished by Kishi, et al.<sup>7</sup> in 1976. This synthesis utilized methyl 2-oxo-4-phthalimidobutyrates as a starting material (see Scheme I) and resulted in a compound indistinguishable from naturally isolated saxitoxin - as assessed by  $^1\text{H-NMR}$  and toxicity studies. The synthesis accomplished the formation of all three saxitoxin rings, and did not employ cyclic compounds as reactants. The pyrrolidine ring was formed first via hydrazine treatment of the carbonyl-protected starting material B. The 6-membered ring of saxitoxin was formed thereafter via condensation with benzyloxyacetaldehyde and silicon tetraisothiocyanate E. The last cyclization was facilitated via the intramolecular reaction of an amide-containing side-chain with a proximal double bond H.

#### OSCILLATOXINS AND APLYSIATOXINS

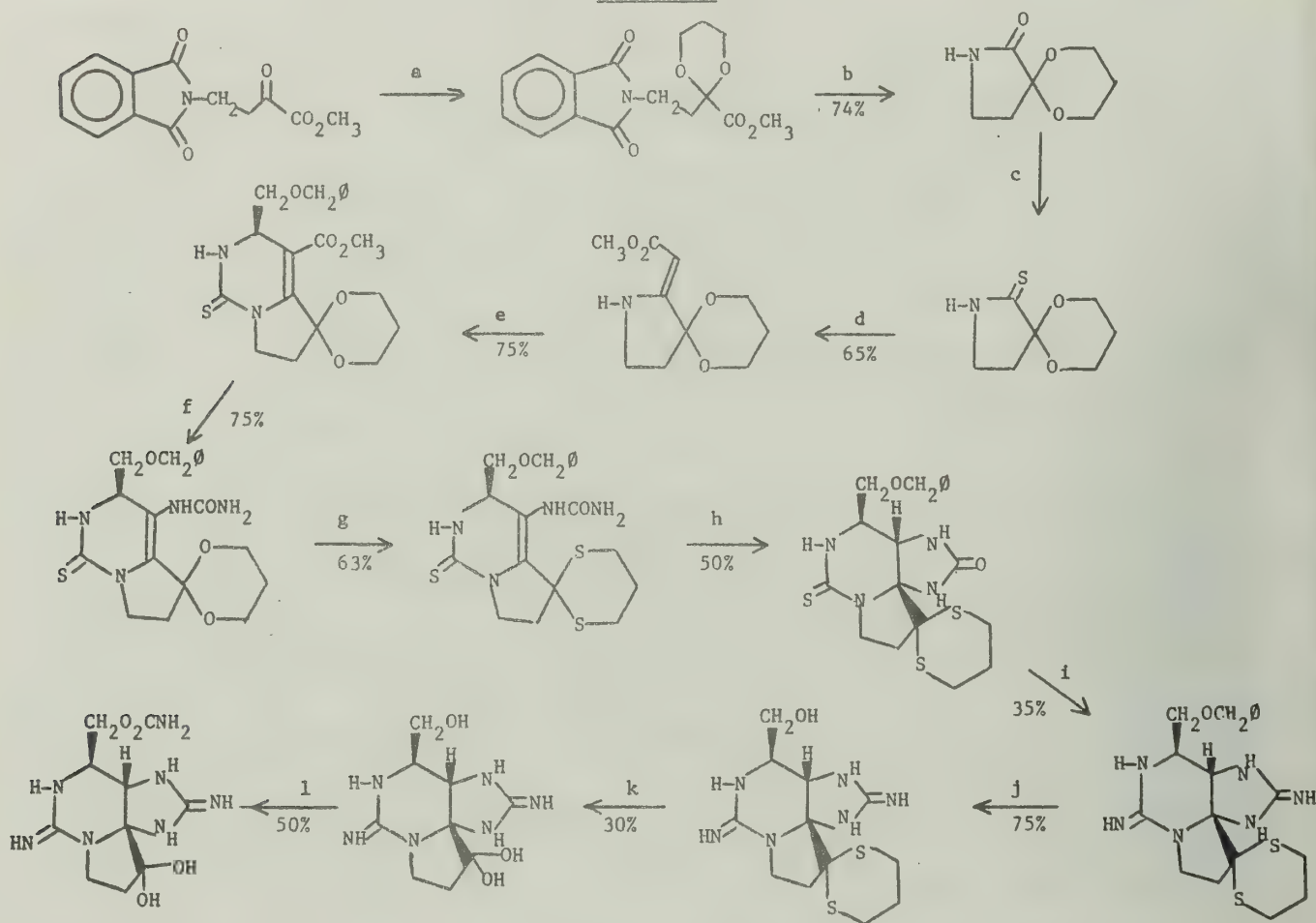
Eight toxic compounds, oscillatoxins and aplysiatoxins, have recently been isolated and identified from the blue-green algae Oscillatoria nigroviridis and Schizothrix calcicola in combined culture 4-11.<sup>13,14</sup> These compounds, in addition to having significant toxicities ( $LD_{\min} = 0.3 \text{ mg/kg}$ , mice, IP), also have mild antineoplastic activity against P-388 mouse leukemia cells,<sup>5</sup> and have been responsible for several outbreaks of severe contact dermatitis among Hawaiian swimmers.<sup>14</sup>

The structures of these compounds were established by mass spectrometry and  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR - and by comparison of the isolates to similar compounds previously

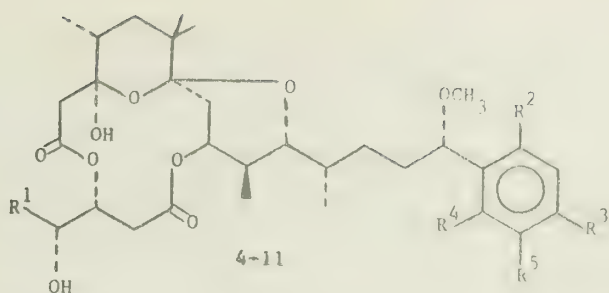


isolated from mollusks and sea hares.<sup>13</sup> Absolute stereochemistry of the compounds was also established via <sup>1</sup>H-NMR NOE experiments, and by studies on degradation products of the materials.<sup>14</sup>

Scheme I



**Conditions:** (a)  $\text{HO}(\text{CH}_2)_3\text{OH}$ , PTSA, Toluene, reflux. (b)  $\text{NH}_2\text{NH}_2$ ,  $\text{CH}_3\text{OH}$ , reflux. (c)  $\text{P}_2\text{S}_5$ , benzene,  $80^\circ\text{C}$ . (d) 1)  $\text{CH}_3\text{COCHBrCOOCH}_3$ ,  $\text{NaHCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ , reflux; 2)  $\text{KOH}$ ,  $\text{MeOH}$ ,  $50^\circ\text{C}$ . (e)  $\text{PhCH}_2\text{OCH}_2\text{CHO}$ ,  $\text{Si}(\text{SCN})_4$ , benzene. (f) 1)  $\text{N}_2\text{H}_4$ ,  $\text{MeOH}$ ; 2)  $\text{NOCl}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-50^\circ\text{C}$ ; 3) benzene,  $90^\circ\text{C}$ ; 4)  $\text{NH}_3$ , benzene. (g)  $\text{HS}(\text{CH}_2)_3\text{SH}$ ,  $\text{BF}_3$ ,  $\text{CH}_3\text{COCN}$ . (h)  $\text{CF}_3\text{COOH}$ ,  $\text{CH}_3\text{COOH}$ ,  $50^\circ\text{C}$ , 18 hr. (i) 1)  $\text{Et}_3\text{O}^+\text{BF}_4^- \cdot \text{NaHCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ ; 2)  $\text{EtCOONH}_4$ ,  $135^\circ\text{C}$ . (j)  $\text{BCl}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ . (k) 1)  $\text{NBS}$ ,  $\text{CH}_3\text{CN}$ ,  $15^\circ\text{C}$ ; 2)  $\text{MeOH}$ ,  $100^\circ\text{C}$ . (l)  $\text{HCOOH}$ ,  $\text{ClSOCN}$ ,  $5^\circ\text{C}$ .

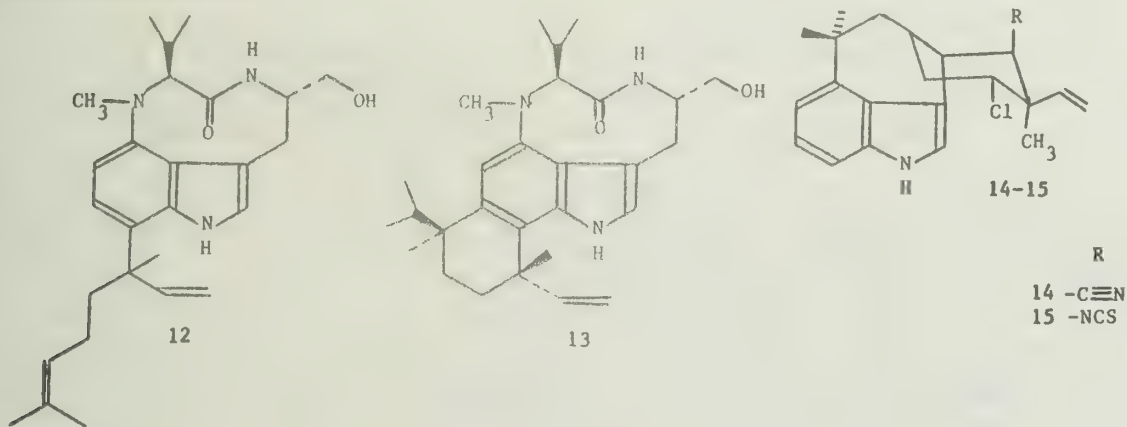


	1 R	2 R	3 R	4 R	5 R
4	Me	Br	H	H	OH
5	Me	H	H	H	OH
6	H	H	H	H	OH
7	H	Br	H	H	OH
8	H	Br	Br	H	OH
9	Me	Br	Br	H	OH
10	Me	H	Br	H	OH
11	Me	Br	Br	Br	OH

### LINGBYATOXIN

Another marine blue-green algal toxin was identified from Lingbya majuscula via  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR (with  $^1\text{H}$  decoupling experiments), absorption spectroscopy, mass spectroscopy, hydrogenation and the Erlich test.<sup>15</sup> Lingbyatoxin 12 has an  $\text{LD}_{100}$  of 0.3 mg/kg (mice, IP), and is similar in structure to teleocidin B 13 isolated from Streptomyces ( $\text{LD}_{50}=0.22$  mg/kg).<sup>15</sup> Further, the stereochemistry of lingbyatoxin was said to be established by comparison of optical rotation data of that of previously isolated 13.<sup>16</sup>

It is interesting to note that similar indole compounds with antimycotic and perhaps toxic properties has also been isolated from the blue-green alga Hapalosiphon intricatus 14, 15.



R  
14 -C≡N  
15 -NCS

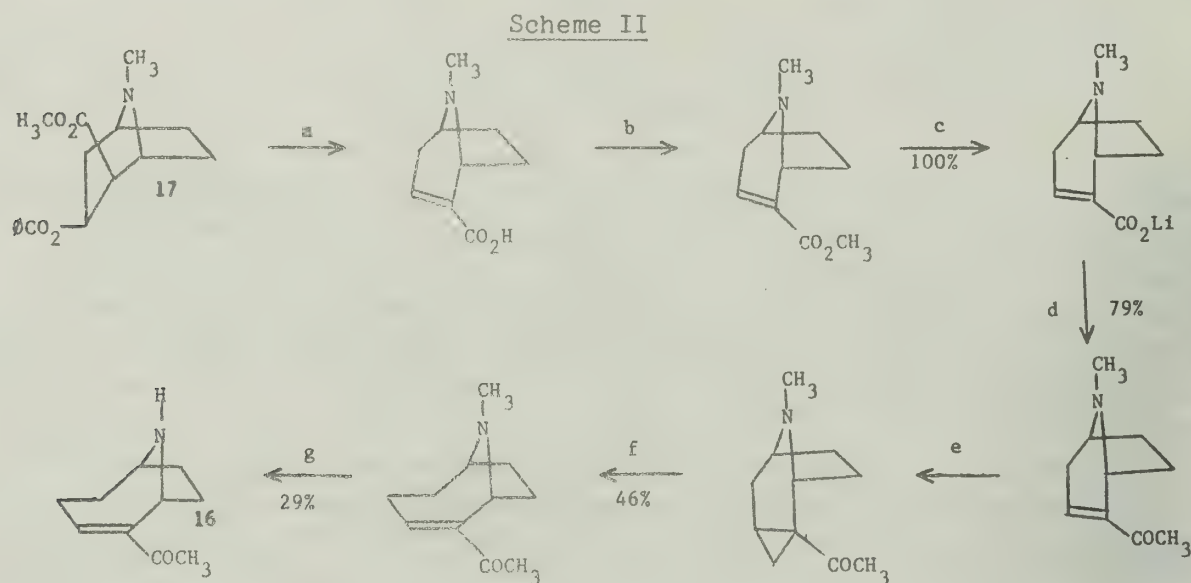
### Freshwater Algal Toxins

#### ANATOXIN

Anatoxin-a 16, a compound similar in chemical structure to cocaine 17, is a toxic material isolated from the freshwater blue-green alga Anabaena flos-aquae.<sup>2</sup> This compound has an  $\text{LD}_{\text{min}}$  of 0.25 mg/kg (mice, IP), and has resulted in significant livestock kills as a result of water supply contamination. It is interesting to note that, although [3.2.1]bicyclic compounds are relatively commonly seen in natural

products, [4.2.1]bicyclic structures are quite rare.<sup>17</sup> The structure of anatoxin-a was assigned by X-ray crystallography in 1972,<sup>18</sup> and was later confirmed by spectroscopy and by comparison to synthetic material (two synthetic routes).<sup>17,20</sup>

Anatoxin-a has been synthesized from cocaine (Scheme II),<sup>20</sup> while dihydroanatoxin-a has been synthesized employing 1-methylpyrrole as a starting



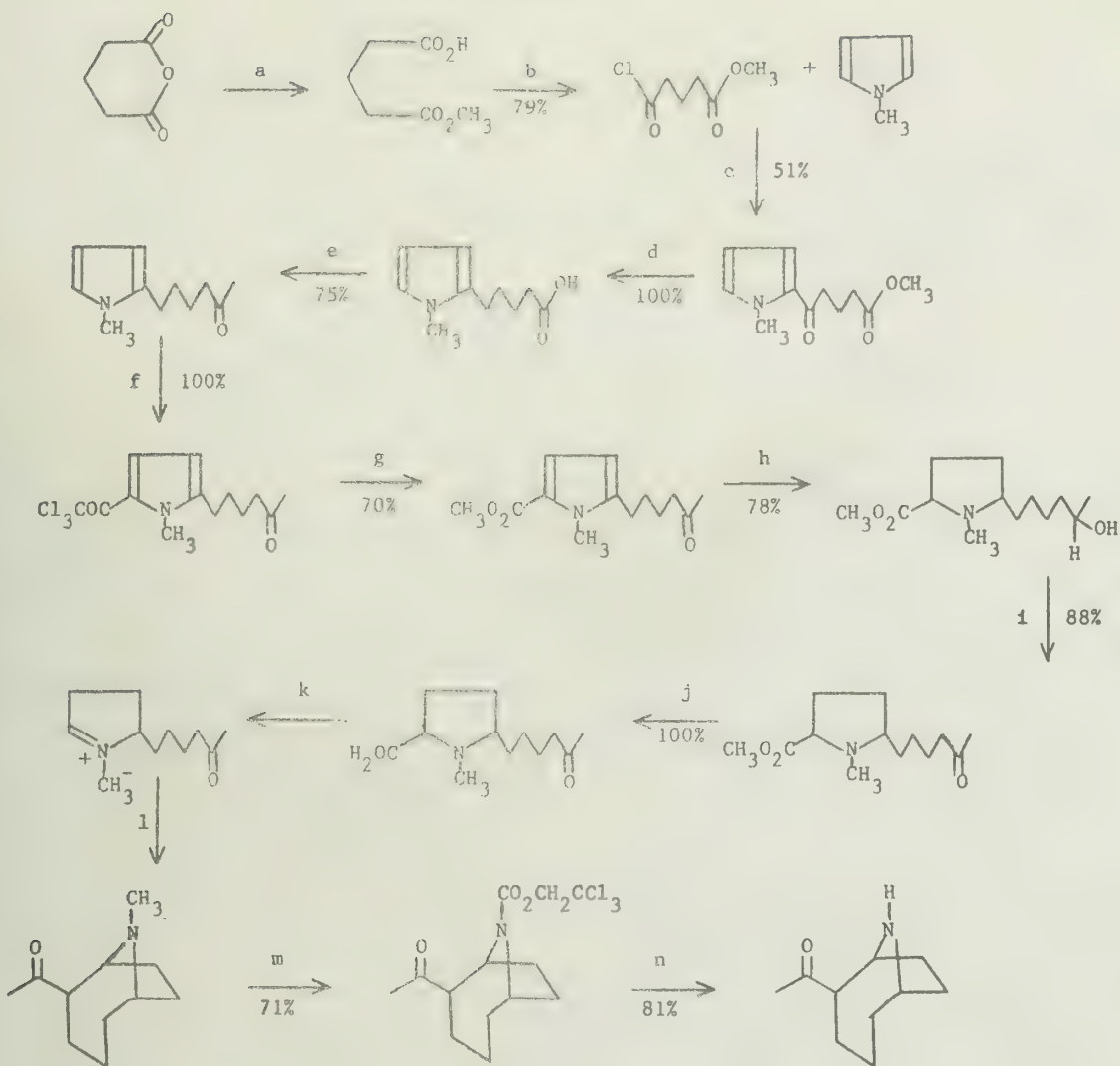
**Conditions:** (a) 12N HCl, reflux. (b) MeOH, HCl, 0°C. (c) 95% CH<sub>3</sub>OH, LiOH, reflux. (d) MeOCH<sub>2</sub>CH<sub>2</sub>OMe, MeLi, 5°C. (e) (CH<sub>3</sub>)<sub>2</sub>S=CH<sub>2</sub>. (f) hν, 20°C, 24 hr. (g) 1) aq. NaOH 2) MeCH<sub>2</sub>OOCN=NCOOCH<sub>2</sub>Me, benzene, reflux; 3) 2N HCl, EtOH, reflux.

material (Scheme III).<sup>17</sup> It is interesting to note that the toxicity of dihydroanatoxin-a is only 10% of that of anatoxin-a,<sup>17</sup> suggesting that the unsaturation of anatoxin-a enhances its toxicity.

The synthesis of anatoxin-a from cocaine (Scheme II) was accomplished by elimination of the benzoate functionality to form a double bond A, followed by addition to the double bond E and finally photolytic ring opening of the cyclopropane ring F to produce the bicyclo[4.2.1] framework. The synthesis of dihydroanatoxin (Scheme III) was accomplished via a somewhat more arduous route employing Friedel-Crafts addition of 4-methoxycarbonylbutanoyl chloride to 1-methyl pyrrole C, various side chain manipulations, and finally by intramolecular cyclization of an iminium salt L to form the bicyclo[4.2.1] framework. Although this synthesis results in dihydroanatoxin-a, other authors have reported a procedure for the conversion of this material to anatoxin-a via bromination and elimination of HBr to form the requisite double bond.<sup>20</sup>



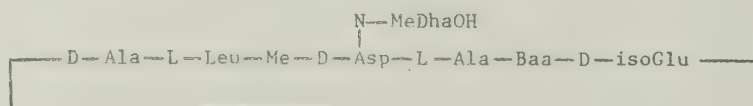
Scheme III



**Conditions:** (a) MeOH, 100°C. (b) SOCl<sub>2</sub>, 70°C. (c) AlCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -40 + 20°C. (d) 1) NH<sub>2</sub>NH<sub>2</sub>, HOCH<sub>2</sub>CH<sub>2</sub>OH, 100°C; 2) KOH, 210°C. (e) 1) LiOH, 40°C; 2) MeLi, THF, 0°C; 3) HCl, 0°C. (f) Cl<sub>3</sub>CCOCl, Et<sub>2</sub>O. (g) NaOMe, MeOH. (h) H<sub>2</sub>, 5% Rh, H<sub>2</sub>SO<sub>4</sub>, MeOH. (i) 1) CrO<sub>3</sub>, H<sub>2</sub>SO<sub>4</sub>; 2) NaHCO<sub>3</sub>. (j) 6 M HCl, 90°C. (k) POCl<sub>3</sub>, 105°C. (l) MeOH, reflux. (m) Cl<sub>3</sub>CH<sub>2</sub>OOCCl, benzene, reflux. (n) Zn dust, AcOH.

# TOXIN BE-4

Toxin BE-4, 18, a cyclic peptide containing a novel amino acid, has recently been identified from a Microcystis aeruginosa freshwater blue-green algal extract.<sup>21,22</sup> This toxin is one of 4 peptide toxins produced by the organism, and has an LD<sub>50</sub> of 56 µg/kg (mice, IP).<sup>22,23</sup> The compound is apparently both neuro- and hepatotoxic.<sup>23</sup> Structural elucidation was accomplished in 1983 via <sup>1</sup>H-NMR with decoupling and NOE experiments, via selective reduction, esterification, hydrolysis and via Edman degradation.<sup>21,22</sup>



18

## Conclusions

The structures and toxicities of several toxins of marine and freshwater blue-green alga were discussed. These compounds constitute a quite diverse group of materials unified only by their moderate to extreme toxicity and by their tendency to produce mainly neural and gastrointestinal effects in mammals. Synthesis for the two most studied toxins, saxitoxin (from marine algae) and anatoxin-a (from a freshwater algae) were also discussed. At present, no biosynthetic studies of the production of these algal toxins are available.

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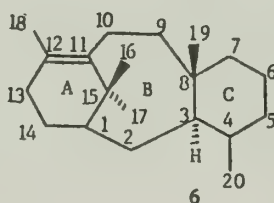
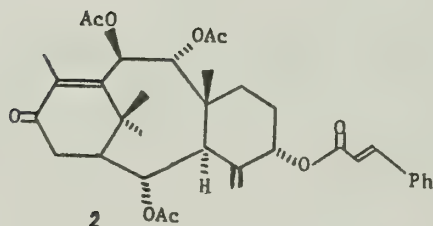
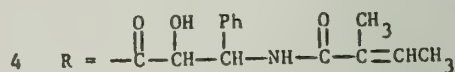
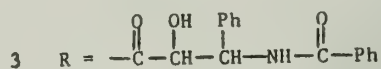
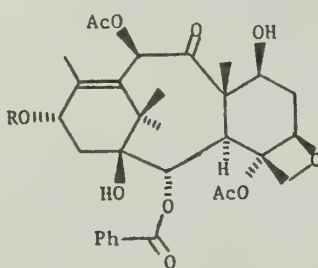
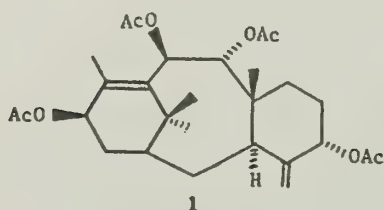


# SYNTHETIC APPROACHES TO THE TAXANE RING SYSTEM

Reported by Du-Jong Baek

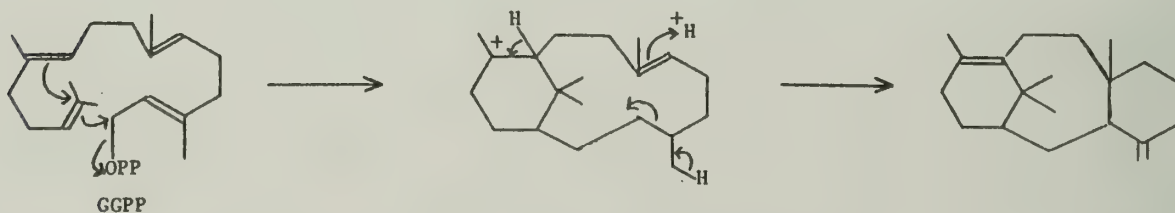
October 31, 1985

The taxanes are a group of diterpene natural products contained in the plants of the Taxaceae family (yew tree). Many related compounds, e.g. Taxusin (1), Taxinine (2), Taxol (3), Cephalomannine (4) and Baccatin III (5), have the unique taxane ring system (6) based on the unusual tricyclo[9.3.1.0<sup>3,8</sup>]pentadecane carbon framework.<sup>1</sup> They are responsible for the poisonous property of the plants (cattle



poison),<sup>1a</sup> and a number of taxanes have recently been shown to exhibit potent anti-leukemia and anti-cancer properties.<sup>2</sup> The biogenesis has been postulated starting from geranylgeranyl pyrophosphate as shown in Scheme I.<sup>3</sup> The biological properties and biogenetic significance in combination with the complex ring structures have made the molecules interesting and challenging targets for total synthesis.

Scheme I



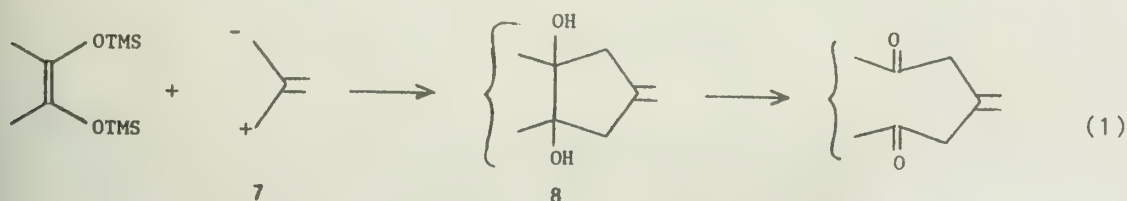
The taxane ring system itself was synthesized only recently,<sup>7,11</sup> although approaches to the synthesis of taxanes using model compounds have been recorded for nearly a decade.

The central problem in taxane synthesis is the construction of bicyclo[5.3.1]undecane AB ring system. Particularly, formation of the eight-

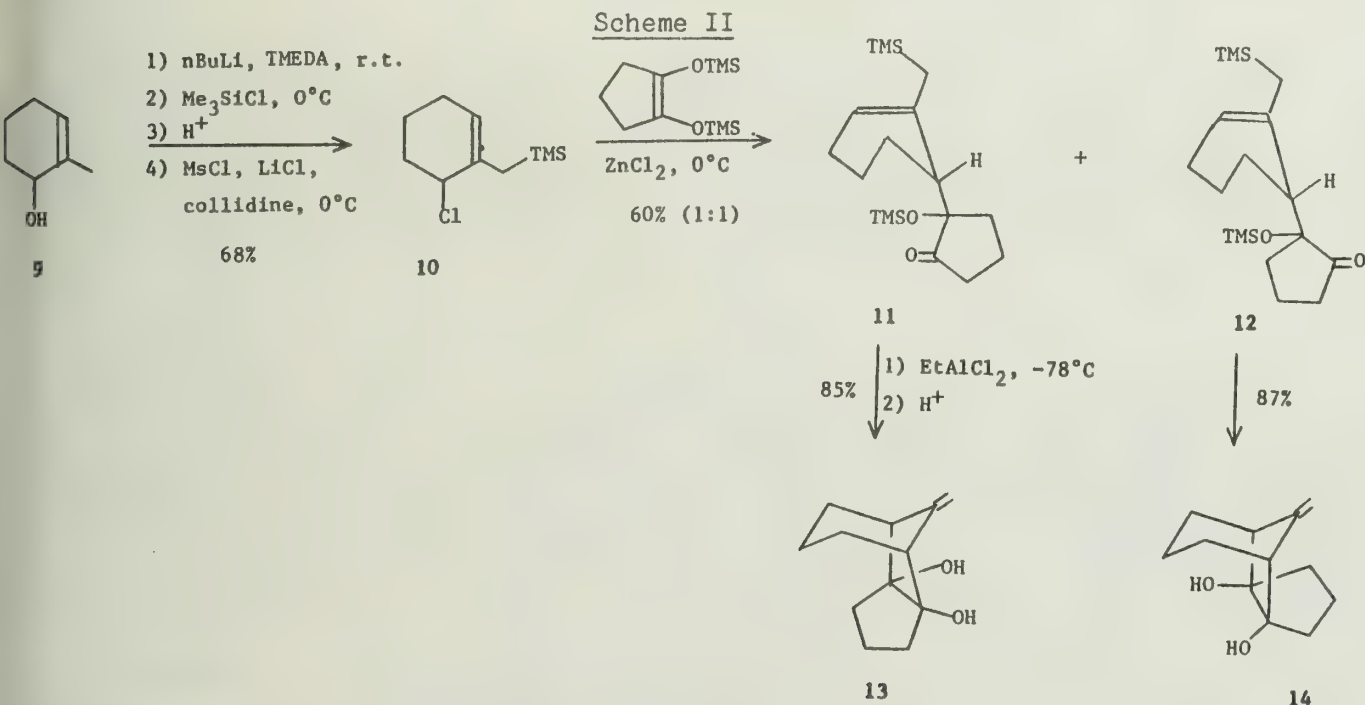
membered B ring is crucial. Several approaches to this problem have been reported: 1) fragmentation reactions,<sup>4-7</sup> 2) anionic oxy-Cope rearrangement,<sup>8</sup> 3) intramolecular Diels-Alder reactions<sup>10-12</sup> and 4) ring contraction.<sup>13</sup> In addition, two as yet unsuccessful approaches are in progress: 1) AC ring combination<sup>14</sup> and 2) biogenetic approach.<sup>15</sup>

### Fragmentation Reactions

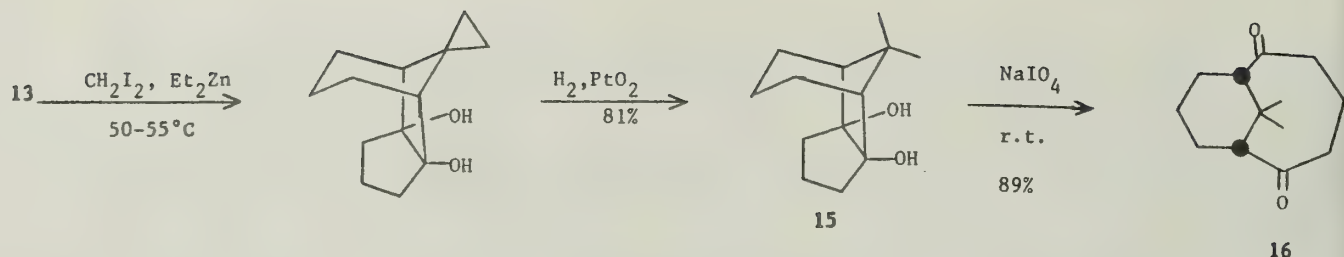
Trost<sup>4</sup> used bifunctional synthon (7) containing electrophilic and nucleophilic centers to form the initial adduct (8). The facile oxidative cleavage of a vicinal diol leads to formation of the B ring, Equation 1.



Trost's approach (Scheme II) began with direct metalation of the allylic alcohol 9 and subsequent chlorination to give the bifunctional conjunctive reagent

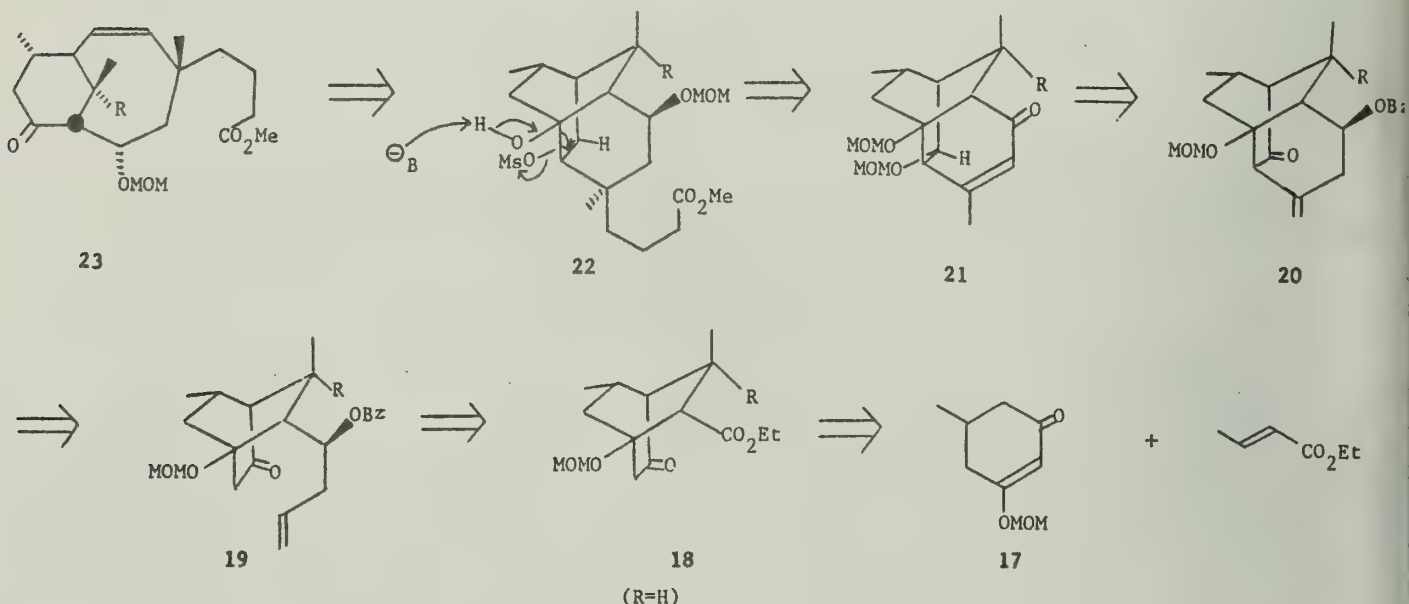


10. The  $\alpha$ -silyloxy ketones 11 and 12 were obtained by the reaction of 10 with 1,2-bis(trimethylsilyloxy)cyclopentene. Ketones 11 and 12 cyclized to give the diols 13 and 14. Before fragmentation by oxidative cleavage (15+16), conversion of the exocyclic methylene group of 13 to a gem-dimethyl group was done by cyclopropanation and hydrogenolysis.<sup>4b</sup>



Another approach to AB ring formation by Yamada<sup>5</sup> employed a Grob fragmentation of tricyclicundecane derivative 22. The retrosynthetic analysis is outlined in Scheme III.

Scheme III



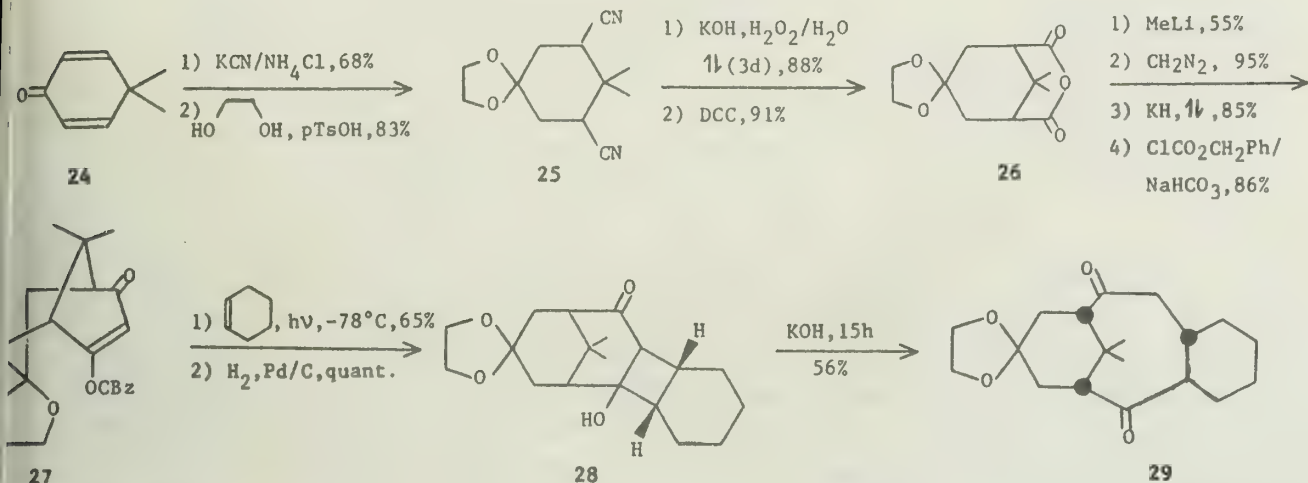
Sequential Michael reaction of the lithium enolate of 17 with ethyl crotonate gave bicyclooctanone 18 which was transformed to the keto olefin 19 by reduction and oxidation of the ester to aldehyde, followed by introduction of an allyl group and protection of the hydroxyl group. The keto olefin 19 was epoxidized, cyclized and dehydrated to give olefin 20. Reduction of ketone group, oxidation of secondary alcohol and subsequent isomerization yielded 21 with proper protection and deprotection. After introduction of the four-carbon unit into the  $\beta$ -position of unsaturated ketone 21 and various functional group manipulations, 21 was transformed to fragmentation substrate 22. Treatment of 22 with potassium hydride followed by methylation produced the bicyclic keto olefin 23.

The third approach by Blechert<sup>6</sup> used a stereoselective [2+2] photocycloaddition to construct the fragmentation precursor 28 (Scheme IV). Dicyano ketal 25 was hydrolyzed and cyclized to give bicyclic anhydride 26 which was then transformed to



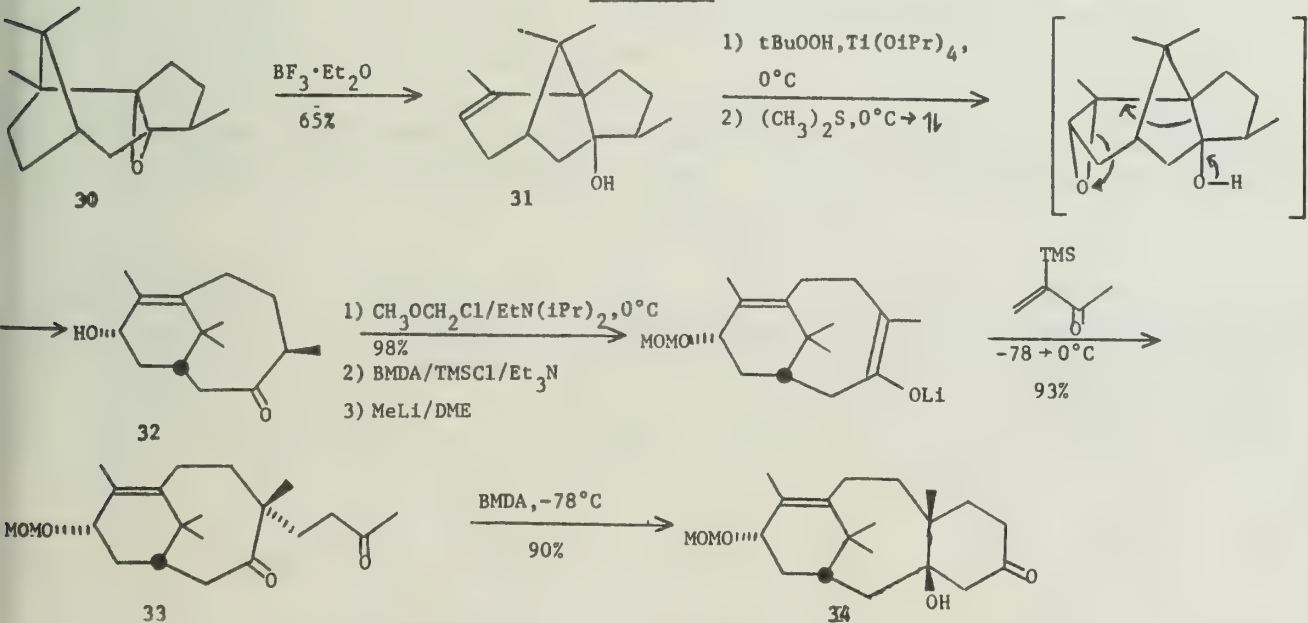
none 27 by methyllithium addition, esterification, Dieckmann condensation and protection. Irradiation of 27 in the presence of cyclohexene and deprotection yielded cycloadduct 28. This arose via  $\beta$ -attack of cyclohexene due to the bulky acetal protecting group. The retroaldol ring opening was easily accomplished to generate tricyclic diketone 29.

Scheme IV



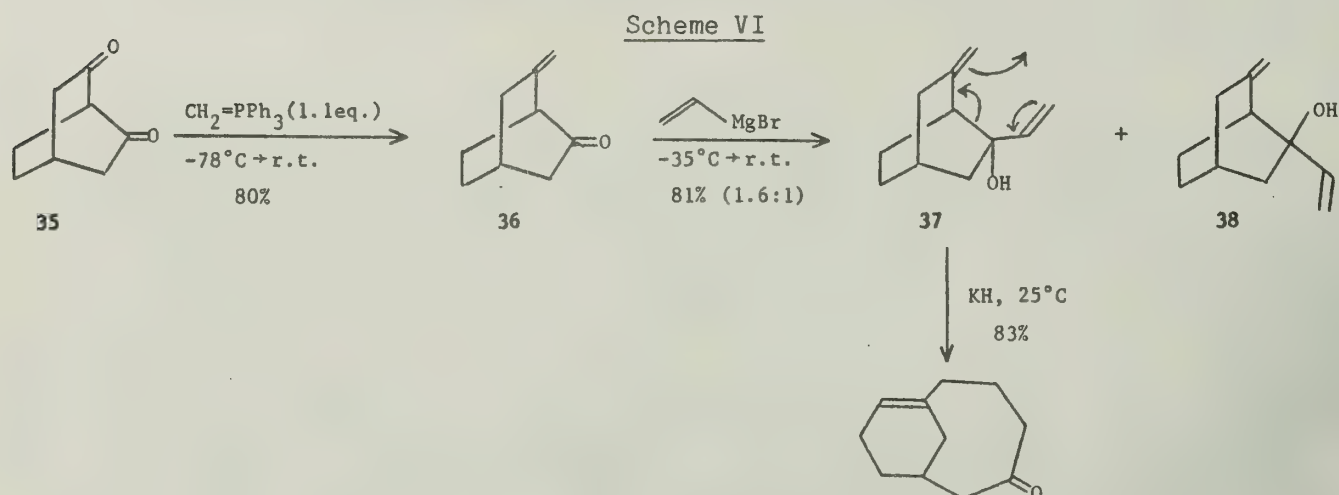
The first synthesis of the taxane ring with the bridgehead double bond was done by Holton<sup>7</sup> from  $\beta$ -patchoulene oxide 30. The key reaction is an epoxidation-derived fragmentation ( $31 \rightarrow 32$ ) to form the eight-membered B ring (Scheme V). Diketone 33 generated by Michael addition was cyclized to form 34 using a magnesium counterion (bromomagnesium diisopropylamide; BMDA). This synthesis requires five steps from readily available, optically active starting material and proceeds in 53% overall yield.

Scheme V



### Anionic Oxy-Cope Rearrangement

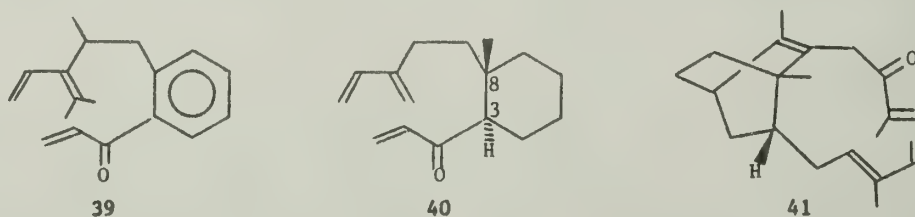
Martin<sup>8</sup> has investigated the [3,3]sigmatropic rearrangement of bicyclic dienol **37** to generate the bicyclo[5.3.1]undecane ring system (Scheme VI). Wittig



methylenation of dione **35** afforded the enone **36** which was then converted to a mixture of dienols **37** and **38**. After separation, **37** was deprotonated with potassium hydride to yield bicyclo[5.3.1]undec-7-en-3-one via an anionic oxy-Cope rearrangement.<sup>9</sup>

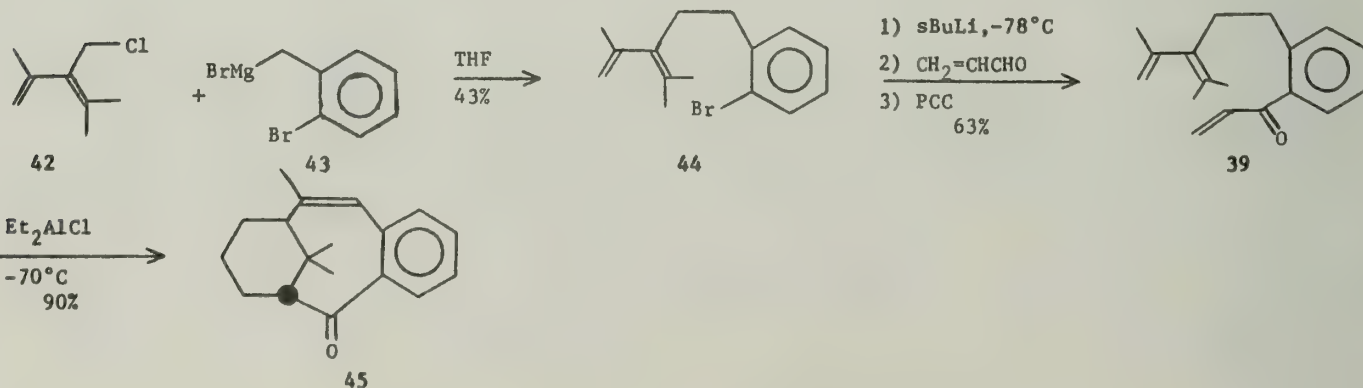
### Intramolecular Diels-Alder Reactions

Different approaches to the concurrent AB or BC ring formation with stereoselectivity were reported using intramolecular Diels-Alder reactions. The key intermediates are the trienones **39**, **40**, or tetraenone **41**.



Shea<sup>10</sup> prepared Diels-Alder substrate **39** as shown in Scheme VII. Reaction of chloride **42** with Grignard reagent **43** gave bromodiene **44**. Subsequent metalation,

### Scheme VII

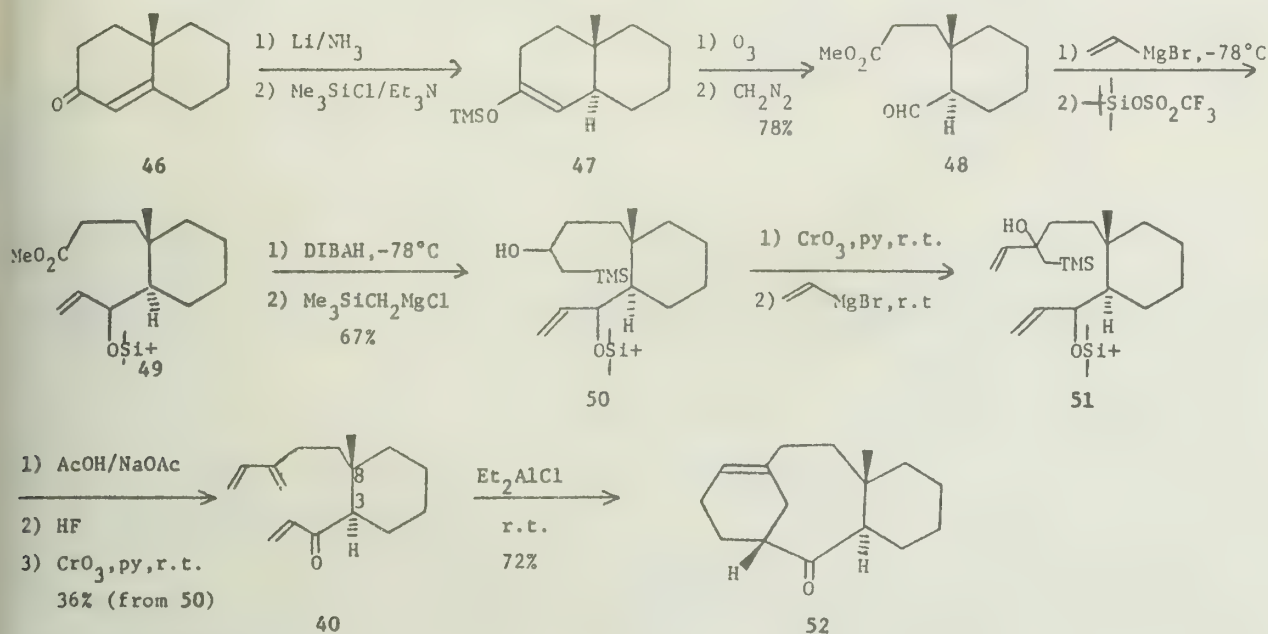


reaction with acrolein and oxidation afforded 39 which generated cycloadduct 45 in the presence of a Lewis acid.<sup>10b</sup>

A similar approach was reported by Jenkins<sup>11</sup> (Scheme VIII) with trienone 40 which has the correct stereochemistry at C3 and C8.

Diels-Alder cyclization of 40 (generated by conventional methods) was induced with a Lewis acid catalyst to give the taxane skeleton 52.

Scheme VIII



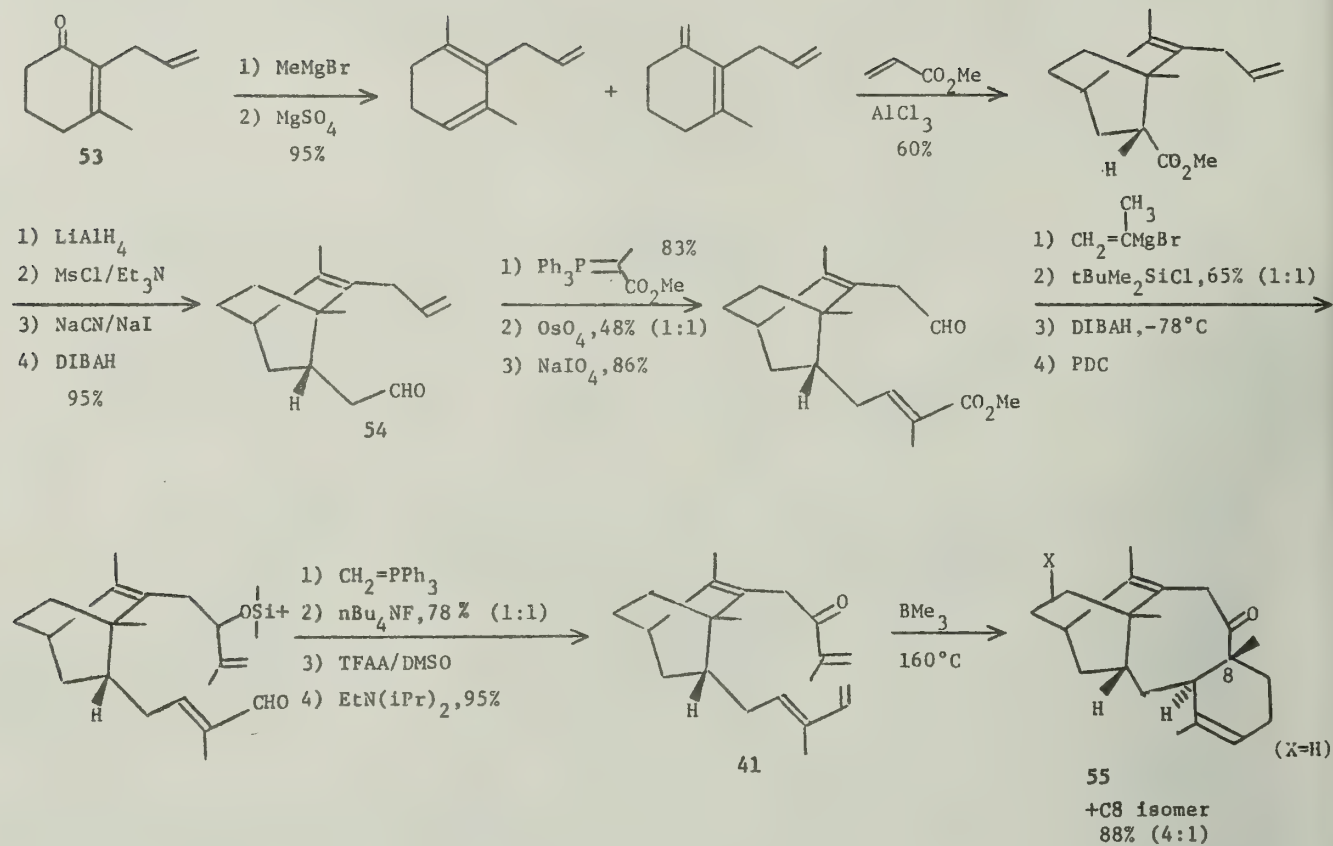
The BC ring formation was carried out by Sakan and Craven<sup>12</sup> utilizing an intramolecular Diels-Alder reaction of 41 which was constructed via dienal 54 (Scheme IX). Methylation of dienone 53, subsequent Diels-Alder reaction and one-carbon homologation gave 54 which was transformed to 41 by conventional manipulations. Thermal cycloaddition of 41 furnished tetracyclic ring system 55. With provision of an appropriate functionality at C20 or C21, the bicyclo[2.2.2]octene can be transformed to the taxane A ring.

### Ring Contraction

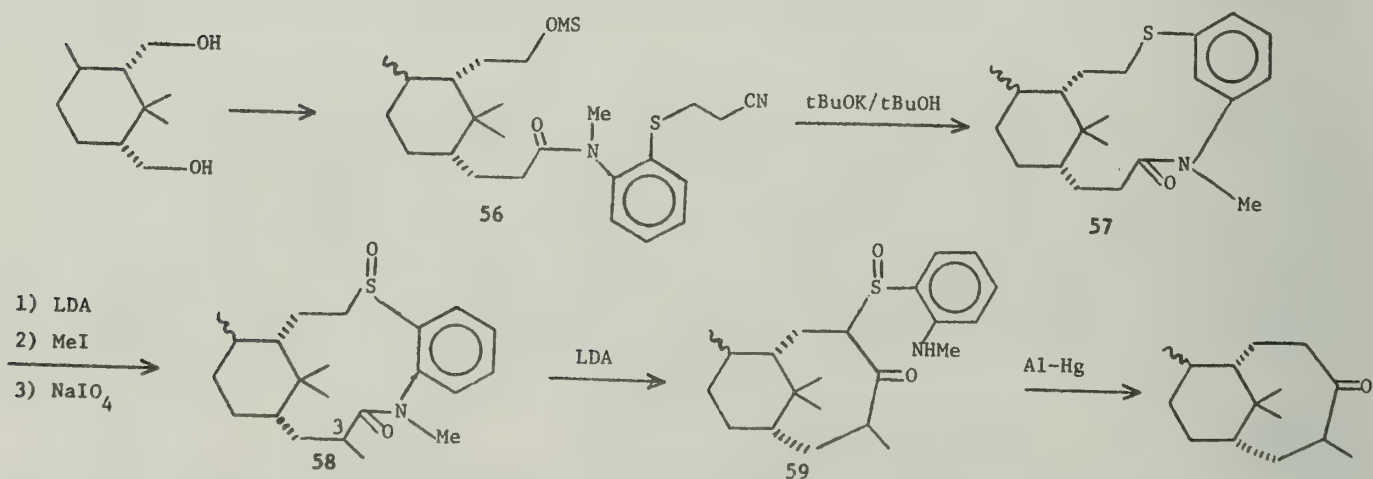
Another type of B ring formation is the cyclization reaction (58→59) investigated by Ohtsuka<sup>13</sup> (Scheme X). Demasking of the thiol protecting group and the concomitant cyclization of mesylate 56 furnished twelve-membered lactam sulfide 57. LDA-promoted transannular cyclization of 58 gave eight-membered keto sulfoxide 59. Reductive desulfurization of 59 yielded the AB portion of the taxane skeleton.



Scheme IX

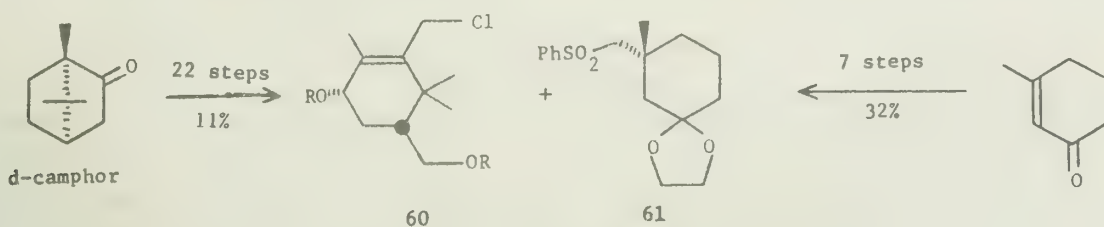


Scheme X



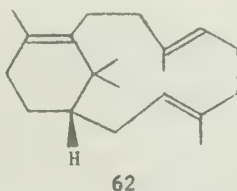
### AC Ring Combination

The construction of B ring by the combination of two optically active segments **60** and **61** was proposed by Kitagawa,<sup>14</sup> though that strategy has not succeeded yet. The left-hand segment **60** was synthesized from d-camphor in 22 steps, 11% overall yield,<sup>14a-c</sup> and the right-hand segment **61** was made from 3-methyl-2-cyclohexen-1-one in 7 steps, 32% yield.<sup>14d</sup>



### Biogenetic Approach

Pattenden<sup>15</sup> suggested another possibility to construct B ring via a transannular cyclization of E,E-verticillene **62** which was considered to be the most likely intermediate in the taxane biosynthesis from GGPP.



However, attempts to induce transannular closure of **62** with  $\text{Et}_2\text{AlCl}$  failed suggesting that different pathways or different geometrical isomers of GGPP may be involved.

### Summary

Eleven approaches to the construction of B ring of taxane skeleton have been reported. Among them, the fragmentation approach by Holton was accomplished with high stereoselectivity in 5 steps, 53% yield. The syntheses via intramolecular Diels-Alder reactions are also successful in 14 steps, 13% yield by Jenkins and in 19 steps, 6% yield by Sakan and Craven. Since the ultimate objective is the total synthesis of the fully functionalized taxanes and proper functional groups can be easily put on the ring systems, the latter two approaches are most promising.

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# FLUORINE AS A SUBSTITUENT IN BIOLOGICALLY ACTIVE MOLECULES

Reported by Susan Sondej Pochapsky

November 14, 1985

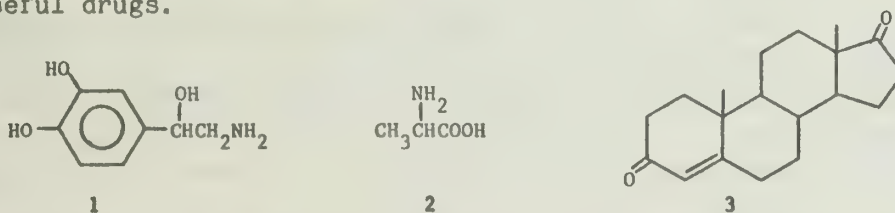
The introduction of fluorine into biologically active compounds to affect bioactivity in a controllable, predictable fashion is becoming increasingly important to medicinal chemists and biochemists. The combination of four different properties make fluorine particularly suitable for this purpose: size, lipophilicity, bond strength, and electronegativity.

Sterically, fluorine resembles hydrogen, possessing a van der Waals radius of 1.35 Å compared to 1.20 Å for hydrogen. This size similarity should allow the substitution of F for H in a biologically active molecule without distortion. Fluorine also possesses the ability to form hydrogen bonds and the substitution of F for H may change the way that a molecule interacts with receptor sites.

Lipophilicity is a property of great importance in drugs and biomolecules because it has a drastic effect on the absorption and transport properties of a compound. Partition coefficients predict that fluorine is more lipophilic than hydrogen, and trifluoromethyl groups are one of the most lipophilic substituents known.<sup>1</sup>

The increased strength of a carbon-fluorine bond relative to a carbon-hydrogen bond (105 kcal/mol and 99.2 kcal/mol, respectively)<sup>2</sup> has been widely exploited. Fluorine has often been used to replace hydrogen when there is an enzymatic reaction involving the abstraction of a proton.

There are two major effects which play significant roles in determining the reactivity of fluorocompounds.<sup>3</sup> The first effect is the inductive withdrawal of electron density from adjacent atoms through the sigma system. The second effect, generally manifested in aromatic systems, involves delocalization of the unshared pair of electrons on fluorine into the pi system of the aromatic ring. These fluorinated analogs frequently exhibit increased potency or selectivity making them potentially useful drugs.



Norepinephrine (1), a chemical neurotransmitter released through the sympathetic nervous system, shows little selectivity between  $\alpha$  and  $\beta$ -adrenergic receptors.<sup>4</sup> Kirk and coworkers synthesized the 2-, 5-, and 6-fluoronorepinephrines (FNE) and have found that 2-FNE is selective for the  $\beta$ -receptor while 6-FNE is selective for the  $\alpha$ -receptor.<sup>5,6,7</sup> In addition, Kirk and coworkers have found predictable alterations in the activities of catechol-O-methyltransferase<sup>8</sup> and monoamine oxidase,<sup>5</sup> both of which are involved in the metabolism of norepinephrine.

Alanine racemase is a pyridoxal-P-dependent enzyme believed to be responsible for providing D-alanine for cell wall biosynthesis. Kollonitsch and coworkers developed three new methods of fluorination: photofluorination,<sup>9</sup> fluorodehydroxylation,<sup>10</sup> and fluorodesulfurization,<sup>11</sup> to selectively introduce fluorine into the  $\beta$ -position of alanine (2), thereby creating an efficient inactivator of the enzyme.<sup>12</sup> Walsh and coworkers synthesized the  $\beta$ -substituted mono-, di-, and trifluoroalanine inhibitors and found that enzyme alkylation of the mono- and trisubstituted derivatives produced stable species causing irreversible inactivation.<sup>13</sup>

Marcotte and Robinson synthesized 19-fluoro and 19,19-difluoro analogs of androst-4-ene-3,17-dione (3) and tested them as inhibitors of the enzyme, aromatase.<sup>14</sup> They found that the monofluoro derivative was easily metabolized, yielding the expected product, estrone. However, the difluoro derivative was metabolically altered to produce a reactive species (believed to be acyl fluoride) which can acylate the enzyme, thereby providing irreversible inhibition.

The interest in incorporating fluorine into molecules designed to mimic biological substrates is likely to continue to grow as more synthetic methods of selective fluorination are developed.

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# SYNTHESIS AND REACTIONS OF N-C YLIDES

Reported by Kaiming Li

November 18, 1985

Ylides are compounds in which a carbanion is attached directly to a positively charged heteroatom. The first synthesis of a nitrogen-carbon ylide (N-C ylide) was reported by Krohnke fifty years ago.<sup>1</sup> Since then, a number of syntheses and reactions of N-C ylides have been reported. The N-C ylides are powerful reagents and intermediates in the synthesis of N-containing heterocyclic compounds. This report is a brief review of the preparations of N-C ylides and their applications in organic synthesis.

## I. Syntheses of N-C Ylides

Three kinds of N-C ylides have been reported: (a) ammonium ylides; (b) azomethine ylides; and (c) nitrile ylides.

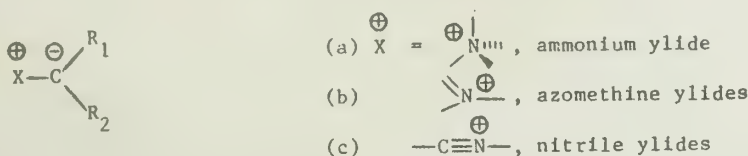
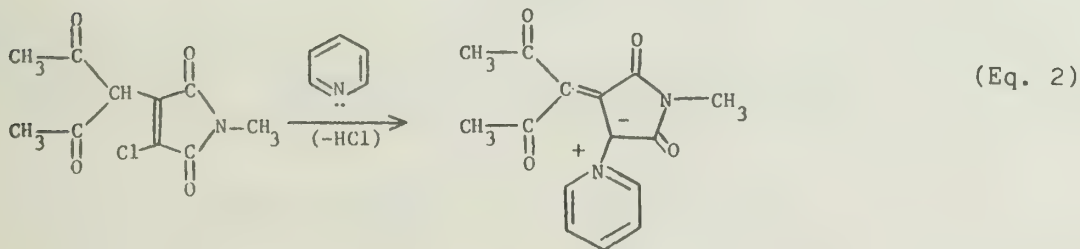
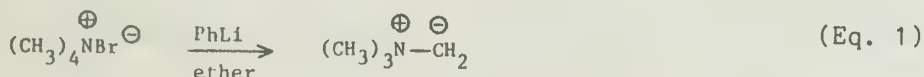
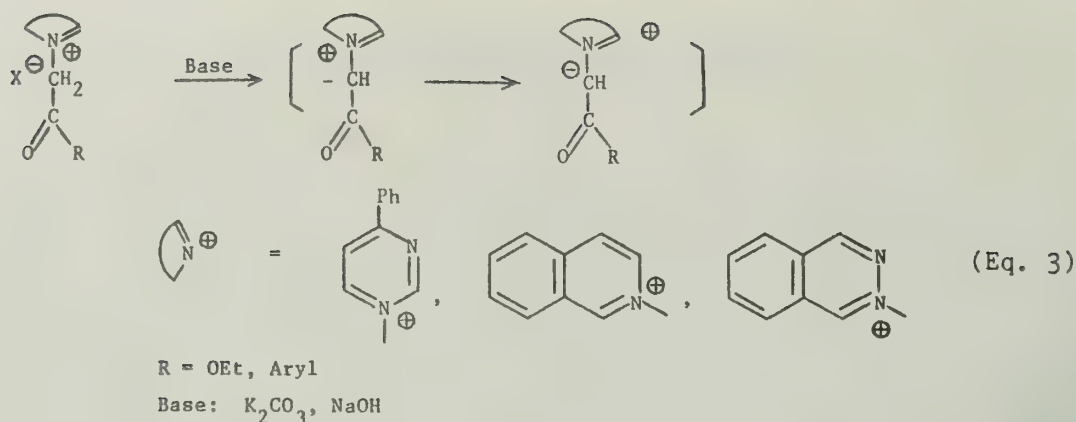


Figure 1

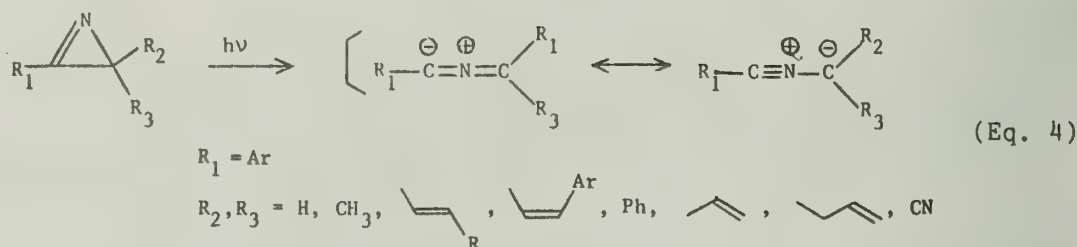
Normally, N-C ylides are not as stable as phosphorus ylides, because a nitrogen atom does not have d-orbitals available for backbonding. Therefore, electron withdrawing groups connected to the negatively charged carbon atom are very important to the stability of N-C ylides.<sup>2</sup> Some N-C ylides are formed only as reactive intermediates, while others can be isolated as stable reagents. The following methods have been used for preparation of N-C ylides.

### (A) Elimination of HX from Ammonium Salts.<sup>3-7</sup>





### (B) Photolysis of 2H-Azirines. <sup>8-13</sup>



Padwa reported that the nitrile ylides produced from azirines have two different geometrical forms: bent and linear.<sup>8</sup> The bent nitrile ylide geometry is calculated to be favored over the linear geometry by at least 10 kcal/mol (Figure 2).<sup>14</sup>

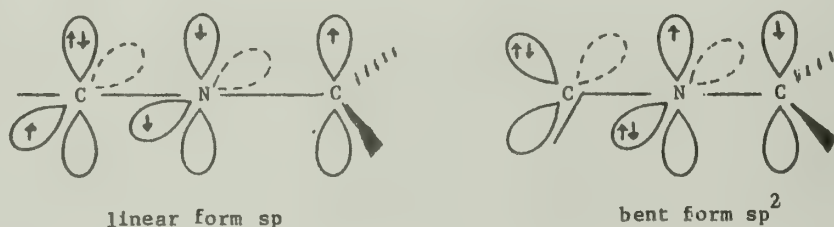
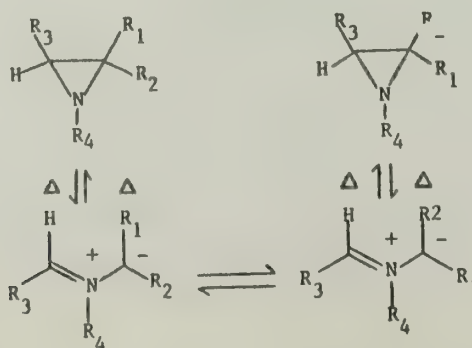


Figure 2.

### (C) Thermolysis of Aziridines

Thermolysis of aziridines produces azomethine ylides.<sup>15,16</sup> Cis-trans isomerization occurs in this process (Scheme I).<sup>16</sup>

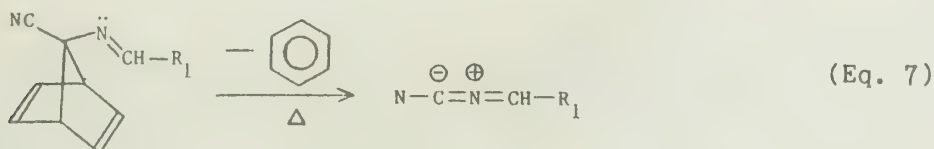
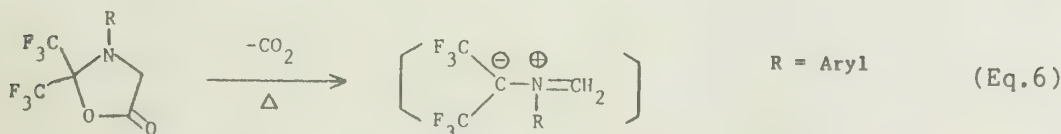
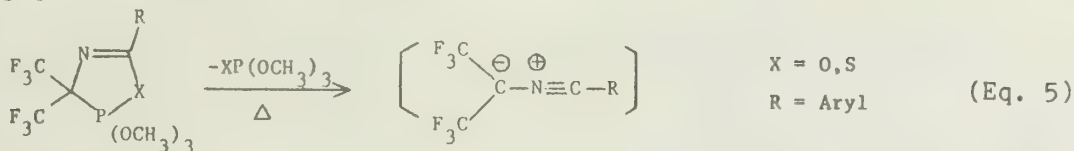
Scheme I



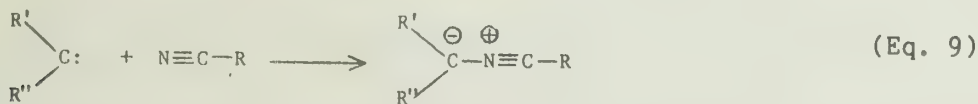
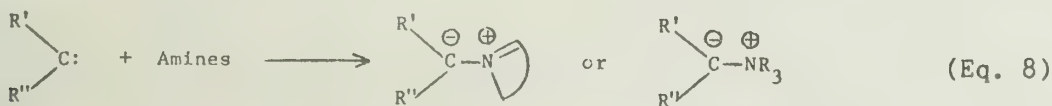


(D) Cycloreversions.<sup>17-22,24</sup>

Some of N-C ylides can be produced by elimination of stable molecules such as CO<sub>2</sub>, OP(OCH<sub>3</sub>)<sub>3</sub> and benzene by thermolysis.

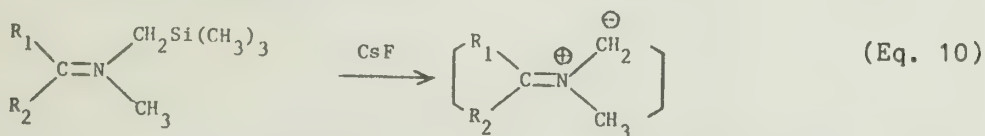


(E) Trapping of Carbenes.<sup>7,25,40</sup>



If the amine is a tertiary amine, a rearranged product can be obtained from the N-C ylide.<sup>40</sup>

(F) Desilylation of  $\alpha$ -Trimethylsilyl Iminium Salts<sup>23,44,45</sup>



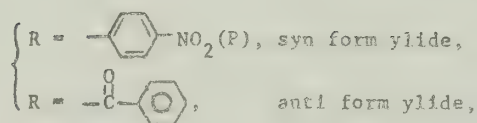
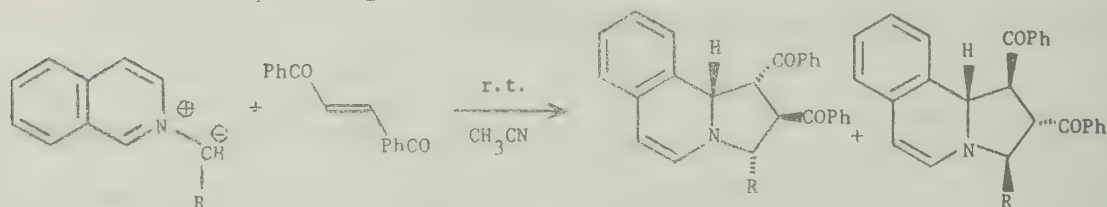
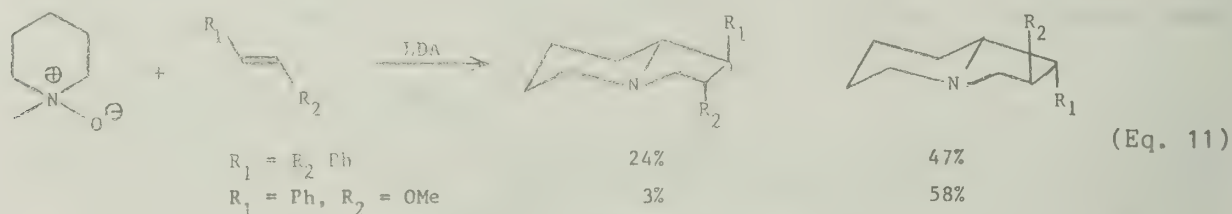
II. Reactions of N-C Ylides

The reactions of N-C ylides have been extensively studied and have been widely employed in the syntheses of N-containing heterocyclic compounds.

(A) 1,3-Dipolar Cycloaddition Reactions of N-C Ylides.<sup>46</sup>

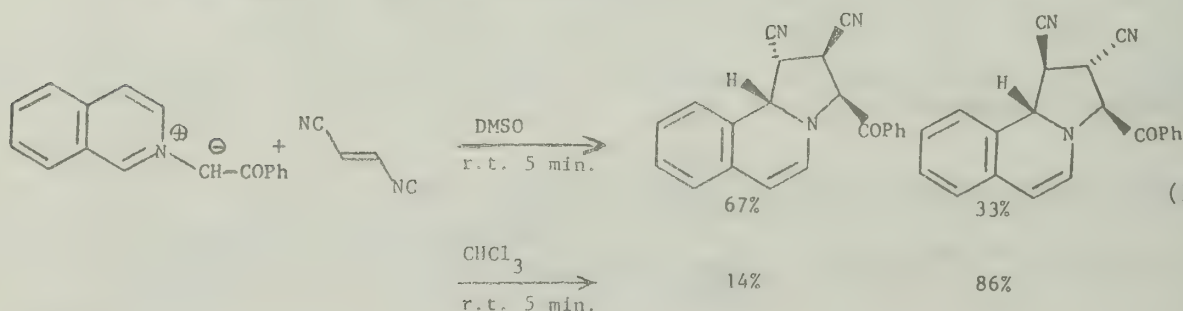
1,3-Dipolar cycloaddition reactions are the most common reactions of the N-C ylides (nitrile ylides and azomethine ylides).

(i) The Stereochemistry of the Cycloaddition Reactions. The 1,3-dipolar cycloadditions of nitrile ylides and azomethine ylides are concerted pericyclic processes. The commonly accepted transition state for nitrile ylides and azomethine ylides is that in which the dipole and the dipolarophile are oriented in two parallel planes.<sup>26</sup> Factors which affect the stereochemistry of the 1,3-dipolar cycloaddition reactions of nitrile ylides and azomethine ylides with dipolarophiles are: the substituents on the dipolarophiles; the conformation (anti form or syn form) of the ylides and the solvent used in the reaction. Examples are shown in Equations 11-13.<sup>28,29</sup>



100%	0%
0%	100%

(Eq. 12)



(ii) The Regioselectivity of the Cycloaddition Reactions. The regioselectivity of the 1,3-dipolar cycloaddition reactions of the nitrile ylides and the azomethine ylides can be rationalized using frontier molecular orbital theory.<sup>6,8,10,26,27</sup> The favored regioisomer is predicted by matching the larger coefficients of frontier orbitals of the dipole and the dipolarophile (Figure 3).

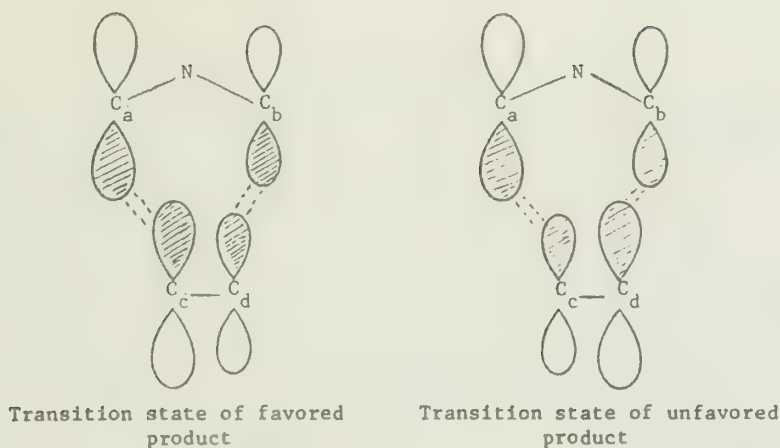
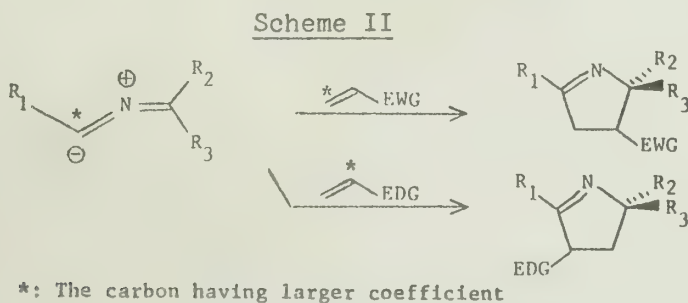
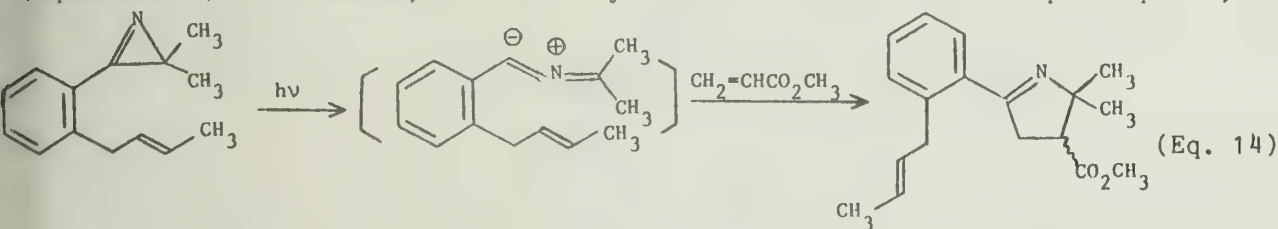


Figure 3.

The size of the coefficients in the dipole ylide and the dipolarophile depend on the substituents (Scheme II).<sup>10, 42</sup>

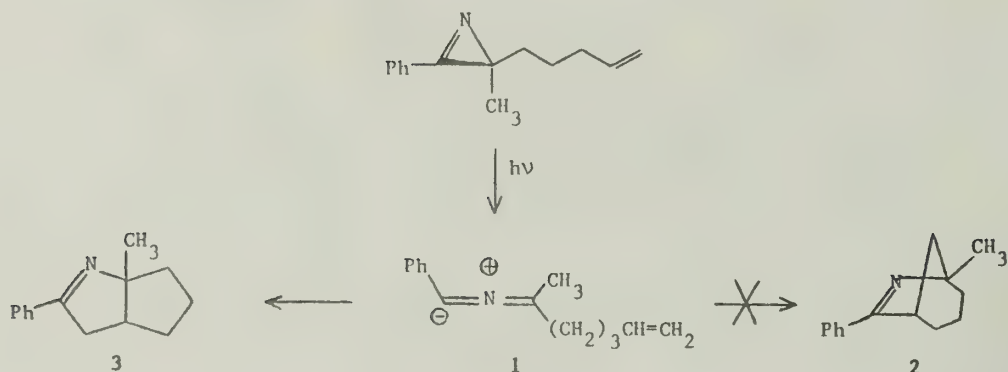


Frontier molecular orbital theory can be used to rationalize the regioselectivity of intermolecular 1,3-dipolar cycloaddition reactions of N-C ylides (Equation 14).<sup>26</sup> However, if the N-C ylide reacts with its own dipolarophile, the



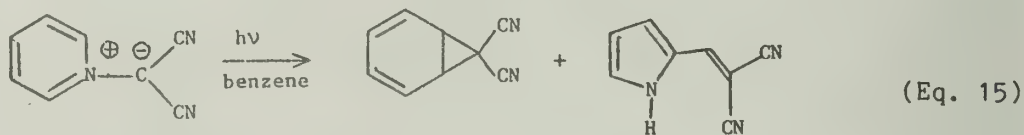
regioselectivity of the intramolecular cycloaddition reaction could not be explained (Scheme III).<sup>10</sup> According to frontier molecular orbital theory, the negatively charged carbon in ylide (1) and the substituted carbon of the double bond in (1) have the larger coefficients. Thus, while the expected product should be compound (2), compound (3) is the only product observed. This was explained by the lack of crowding in the transition state for compound (3).<sup>10</sup>

Scheme III

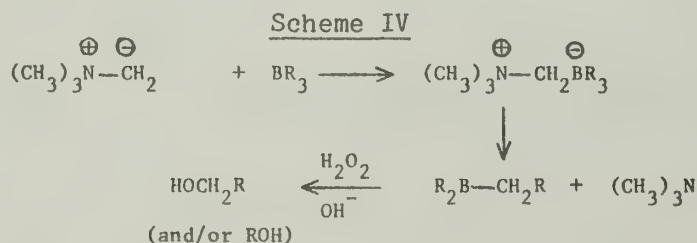


(B) Rearrangement Reactions Involving N-C Ylides

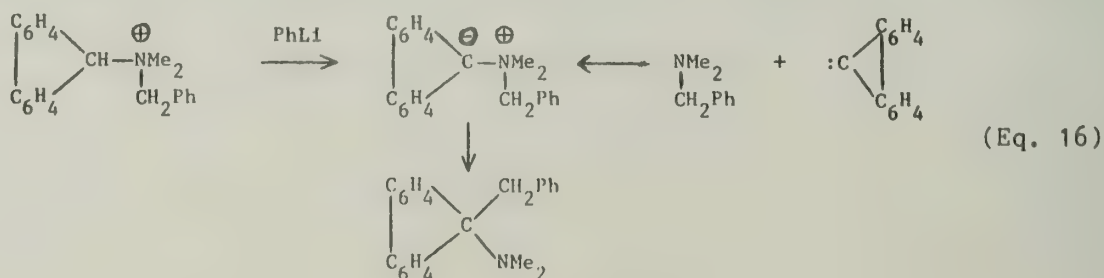
(a) Thermal and Photochemical Rearrangements. The rearrangement reactions of N-C ylides can occur under both thermal (Scheme I)<sup>16</sup> and irradiation condition (Equation 15).<sup>30</sup>



(b) Rearrangement Reactions with Boranes. Trimethylammonium methyllide reacts with organoboranes to produce the homologated organoborane along with trimethylamine.<sup>36</sup> Oxidation of the organoborane with hydrogen peroxide produced alcohols in 22-63% yields (Scheme IV).



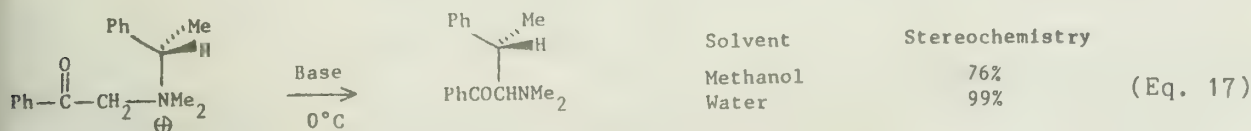
(c) The Stevens Rearrangement of N-C Ylides. Wittig reported a Stevens rearrangement reaction in 1944 (Equation 16)<sup>37</sup> In 1952, Bamford and Stevens obtained the same compound from the reaction of carbene with tertiary amines.<sup>38</sup>





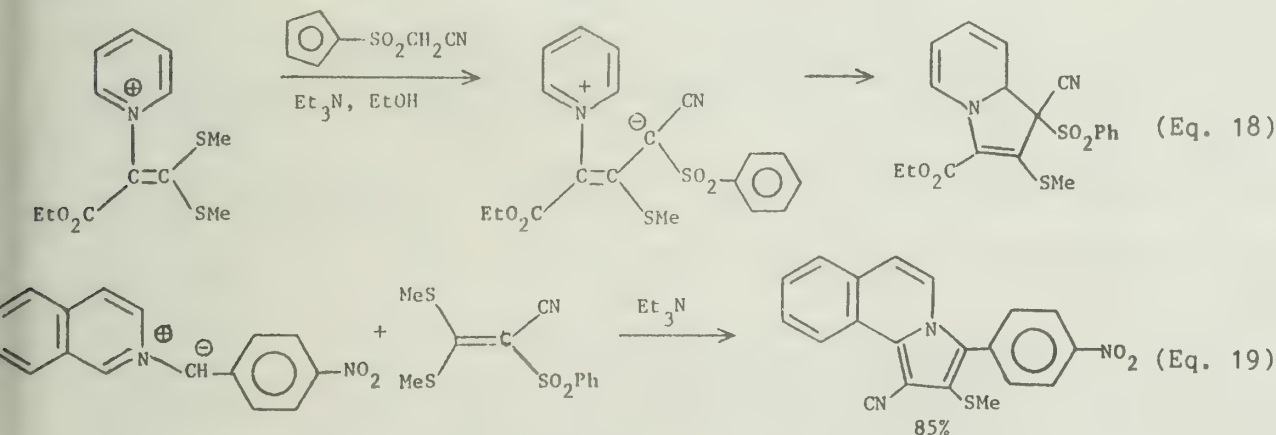
In 1974 Dewar<sup>39</sup> reported the Stevens rearrangement of the ammonium ylide  $(\text{Me}_3\text{N}^+\text{CH}_2^-)$ . MINDO/3 calculations provided a low activation energy for the conversion of  $(\text{CH}_3)_3\text{N}^+\text{CH}_2^-$  into  $\text{Me}_2\text{N}-\text{CH}_2\text{CH}_3$  (17 kcal/mol). The radical pair mechanism, however, was not ruled out by the calculation.<sup>39</sup>

In 1983, the stereoselectivity and the mechanism of the Stevens rearrangement of acyl-stabilized ammonium ylides were investigated by Ollis and coworkers.<sup>41</sup> The stereoselectivity of the rearrangement reaction was found to be related to the solvent viscosity and a radical pair mechanism of the rearrangement was proposed (Equation 17).



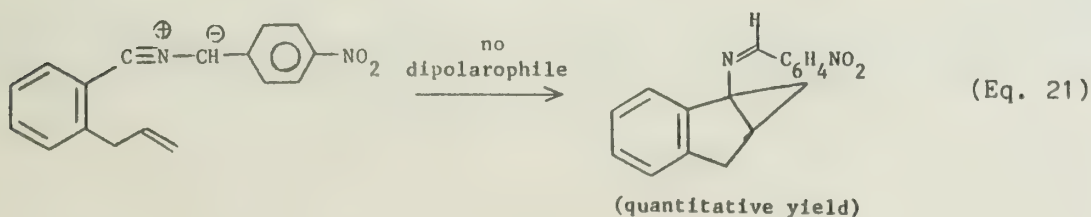
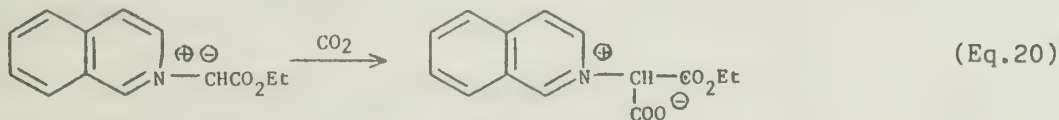
### (C) Electrocyclic Reactions of N-C Ylides

N-C ylides react with active methylene compounds in the presence of a base. Electrocyclic reactions can occur yielding N-containing, novel, cyclic-fused compounds (Equations 18,19).<sup>32,33,34,35</sup>



### (D) Other Reactions of N-C Ylides

Nucleophilic substitution,<sup>7</sup> dimerization<sup>28,43</sup> and 1,1-cycloaddition<sup>26</sup> of N-C ylides have also been reported (Equation 20,21).



## Summary

The highly reactive N-C ylides can be prepared from ammonium salts, azirines and aziridines. A number of reactions of N-C ylides, such as 1,3-dipolar cycloaddition reactions, thermal and irradiation rearrangements and the reactions with electrophiles, have been studied and have been used in the syntheses of organic compounds, especially N-containing, five-membered ring compounds.

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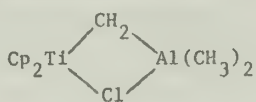
# SYNTHESIS, MECHANISM, AND USES OF THE TEBBE REAGENT

Reported by Anne Parson Wallin

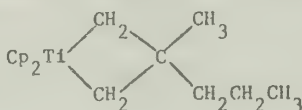
November 21, 1985

## Introduction

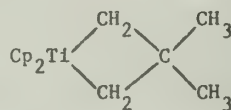
Methylenation and alkyldienation of ketones and aldehydes via the Wittig reaction is a well established transformation in organic synthesis. Unfortunately the Wittig reaction does not normally proceed with carboxylic acid derivatives,<sup>1</sup> and due to the basic nature of the reagent, often results in the loss of stereochemistry at enolizable centers.<sup>3</sup> Recently  $\mu$ -chloro- $\mu$ -methylenebis-(cyclopentadienyl)-titanium dimethylaluminum (the "Tebbe reagent" 1), known to promote olefin



1



2



3

methathesis, has been shown to be an effective methylenation reagent for ketones, aldehydes, lactones, amides, imides, and allenes.<sup>2-8,11,12</sup> Acid chlorides react to give methylene titanium enolates without isomerization or racemization at the  $\alpha'$ -position.<sup>9,10</sup>

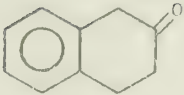
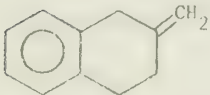
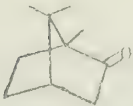
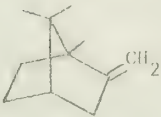

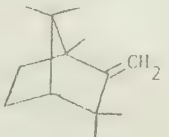
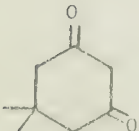
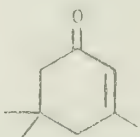
Formation of the reagent is believed to occur through proton transfer of  $\text{Cp}_2\text{TiMeCl} \cdot \text{AlMe}_3$  in a six-membered ring transition state.<sup>13</sup> The reactive intermediate, like that in olefin methathesis, is thought to be a titanium carbene.<sup>12-17</sup> A new and convenient in-situ preparation of 1 should encourage its widespread use in synthesis as a facile and regiospecific methylenating agent.<sup>15</sup>

## Use of 1 With Ketones

Ketones readily undergo methylenation, and Table I shows a variety of ketones which have been shown to give methylenation products by Grubbs and co-workers.<sup>2</sup> Highly enolizable ketones usually give poor yields with Wittig reagents, but even  $\beta$ -tetralone gives a good yield of the desired olefin. The low yield for  $\beta$ -fenchone is presumed to be a steric effect. Another problem, common to Wittig reactions which is overcome by the use of 1, is epimerization at the  $\alpha$ -position. Ireland reports the retention of configuration at the  $\alpha$ -center in a Lasalocid A precursor shown in Scheme I.<sup>3</sup> Reaction of 1 with  $\alpha$ -trisubstituted ketones does not yield olefins but the titanium enolates as shown in Table II.<sup>2</sup> Grubbs and co-workers believe it is the steric crowding at the  $\alpha$ -position which prevents formation of the oxymetallacycle necessary for methylenation.



Table I

Ketone	Product	Yield Using:	
		1	2
		70%	84%
		70%	87%
		20%	0%
		--	70%

Scheme I

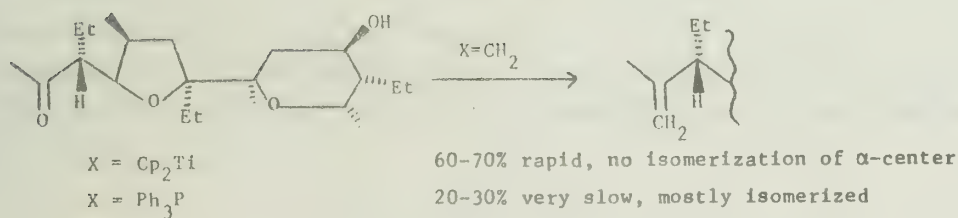



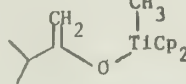
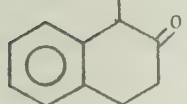
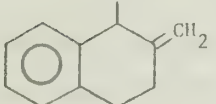
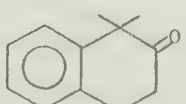
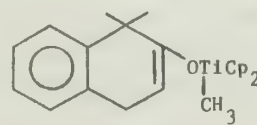


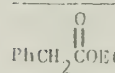
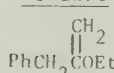
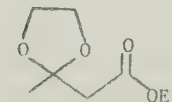
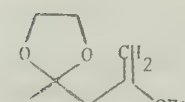
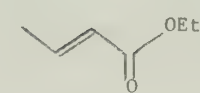
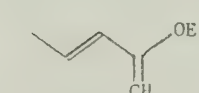
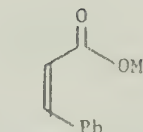
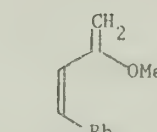
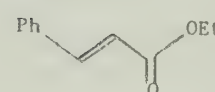

Table II

Substrate	Product	Substrate	Product
			
			
	Yields >95%		Yields 85-90%

### Use of 1 With Esters and Lactones

In 1980 Grubbs and co-workers reported the use of 1 in the methylenation of a wide variety of esters, shown in Table III, in very good yield.<sup>4</sup> It is important to

Table III

Substrate	Product	Yield
		90%
		87%
		82%
		79%
		96%

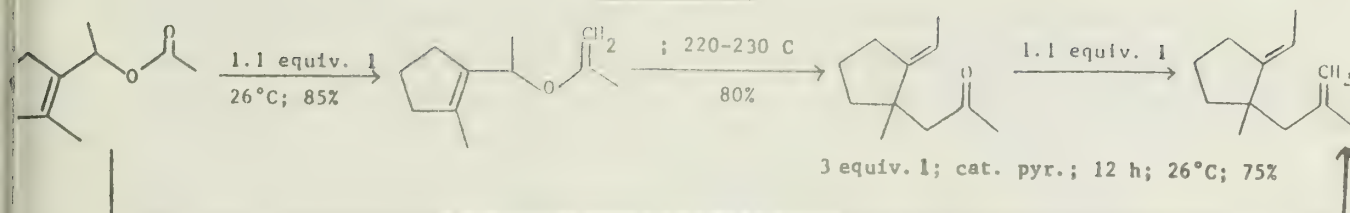
note that the reaction tolerates both olefin and ketal functionalities. In addition olefins retain both their stereochemistry and position. Pine and co-workers prepared a series of para-substituted methyl benzoates to investigate electronic effects of the reaction.<sup>5</sup> They report small rate differences when the reaction is carried out in the absence of a Lewis base, but as shown in Scheme II the yields are

Scheme II



not effected. Pine and co-workers also demonstrated that structural differences in the alcohol moiety are also well-tolerated.<sup>5</sup> They noted that a tert-butyl group results in a dramatic decrease in yield, again presumably a steric effect. When two equivalent ester groups are present a statistical mixture of mono and dimethylenation results. However, if two equivalents of **1** are used the dienol ether is formed in good yield.<sup>5</sup> Stevenson and Bryson have used the Tebbe reagent in conjunction with a Claisen rearrangement in a one-pot synthesis of 1,5-dienes as depicted in Scheme III.<sup>6</sup> It is notable that the one-step synthesis proceeds under milder conditions and in better yield (75%) than the stepwise alternative (61.2%).

Scheme III



Grubbs and co-workers have also demonstrated that **1** reacts in very good yield with lactones as shown in Table IV.<sup>4</sup> Paquette and co-workers have used the Tebbe reagent to synthesize an enol ether which then undergoes Claisen rearrangement in good yield.<sup>7</sup>

Table IV

Substrate	Product	Yield
		85%
		85%

#### Use of **1** With Amides and Imides

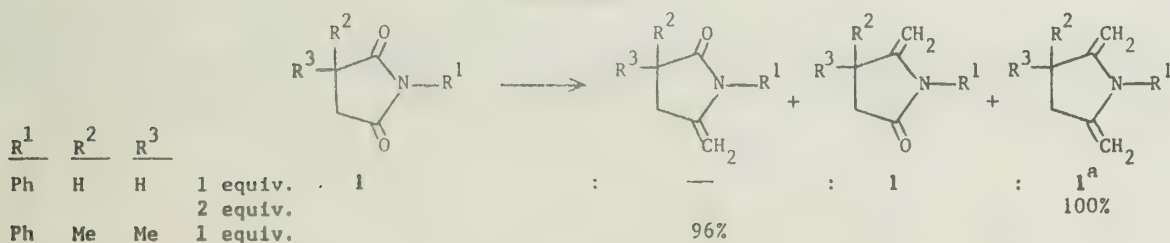
Amides readily undergo methylenation with the Tebbe reagent even in the absence of a Lewis base such as THF or pyridine. Pine and co-workers have prepared enamines from amides as shown in Table V.<sup>5</sup>

Table V

Substrate	Product	Yield
		76%
		97%

Imides undergo methylenation as demonstrated by Cannizzo and Grubbs, but steric hindrance is a significant problem,<sup>8</sup> Table VI. Apparently quaternization of

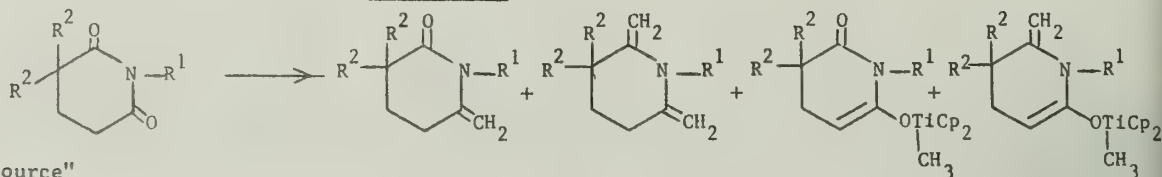
Table VI




a) nmr ratio

an  $\alpha$ -carbon not only improves the regioselectivity of the reaction but also helps stabilize the resulting methylene-pyrrolidinone. Glutarimides are very sensitive to the steric environment of the carbonyl and in several cases titanium enolates were observed.<sup>8</sup> Table VII.

Table VII



<u>R<sup>1</sup></u>	<u>R<sup>2</sup></u>	<u>"Ti source"</u>	
Ph	Me	1 equiv.	3 0
Ph	H	1 equiv.	3 0
	Me	1 equiv.	3
CH <sub>2</sub> Ph	Me	1 equiv.	1
Me	Me	1 equiv.	3

a) nmr ratios

### Use of 1 With Acid Chlorides

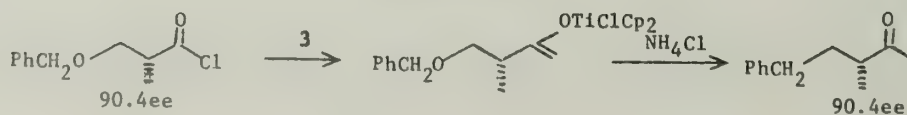
Acid chlorides upon treatment with 1 give titanium enolates as did  $\alpha$ -trisubstituted ketones and some glutarimides.<sup>9</sup> The presence of chloride, a good leaving group, is postulated to be responsible for the formation of the enolates. Table VIII contains several examples of methyl ketones formed after acidic work-up.

Table VIII

<u>Acyl Chloride</u>	<u>Product</u>	<u>Yield (%)</u>
decanoylchloride	2-undecanone	47
phenylacetylchloride	phenylacetone	35
benzoylchloride	acetophenone	42
o-methylbenzoylchloride	o-methylacetophenone	47
p-methylbenzoylchloride	p-methylacetophenone	64
m-methylbenzoylchloride	m-methylacetophenone	49
m-methoxybenzoylchloride	m-methoxyacetophenone	59

The absence of any isopropenyl compounds indicates that the methyl ketone was formed during aqueous work-up. Stille and Grubbs have also reported the synthesis of methyl ketones from acid chlorides using 3.<sup>10</sup> In addition, Stille and Grubbs have shown that there is no racemization at the  $\alpha$ -position (Scheme IV). They also report the trapping of the phenylacetone titanium enolate with benzaldehyde in 69% yield.

Scheme IV

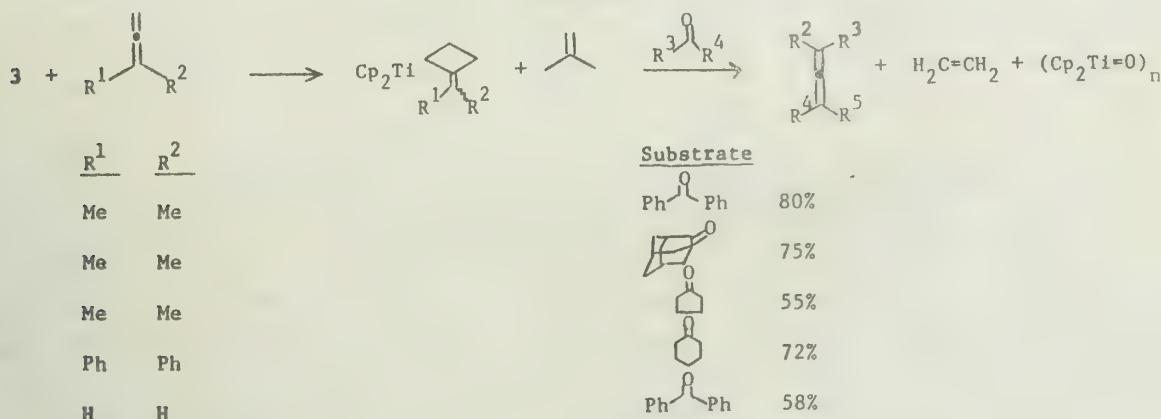




### Use of 3 With Allenes

The Tebbe reagent also reacts with carbon-carbon double bonds. Buchwald and Grubbs have used this methodology to synthesize di-, tri-, and tetrasubstituted allenes according to the reaction depicted in Scheme V.<sup>11</sup> The yields are good to excellent, and the reaction provides an easy alternative to standard methods.

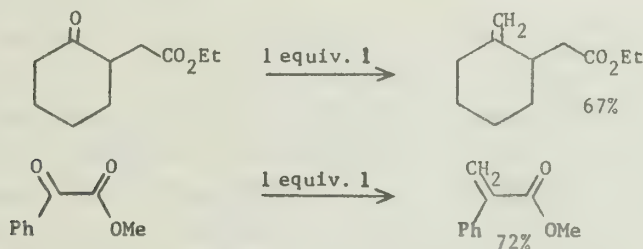
Scheme V



### Selective Methylenation

Ketones undergo methylenation faster than esters. Pine and co-workers have treated the keto-esters shown in Scheme VI with 1 equivalent of 1 and observe only

Scheme VI

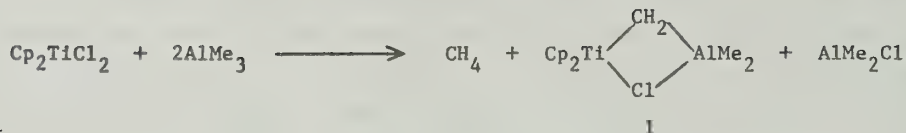


methylenation of the ketone.<sup>5</sup> In addition, Buchwald and Grubbs report that an equimolar solution of acetophenone and methyl benzoate yielded  $\beta$ -methylstyrene and  $\beta$ -methoxystyrene in a ratio of 25-30:1.<sup>11</sup> Ethyl succinyl chloride reacts to give the corresponding keto-ester in 89% yield indicating that acid chlorides also react much faster than esters.<sup>10</sup>

### Mechanism for the Formation of 1

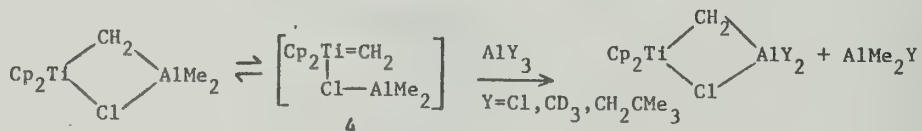
The overall reaction leading to 1 is depicted in Scheme VII. In their initial report Tebbe and co-workers<sup>12</sup> demonstrated that the equilibration of 1 with various

Scheme VII



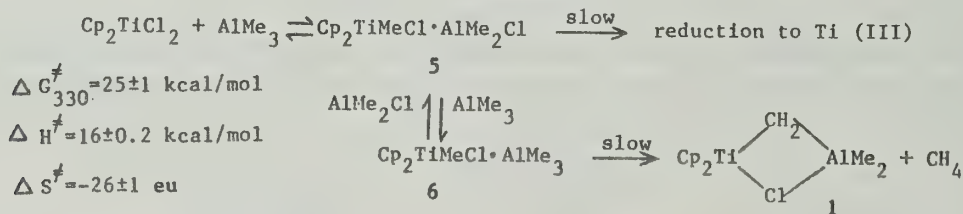
trialkyl- and trihaloaluminum reagents showed exchange of the methyls leaving the methylene group unchanged. This led them to propose the following mechanism, Scheme VIII, and postulate that 4 might be the active reagent. Grubbs and co-workers have

Scheme VIII



further investigated the formation of 1 from titanocene dichloride and trimethylaluminum, Scheme IX.<sup>13</sup> They found the reaction to be second order. Complex 5 is

Scheme IX

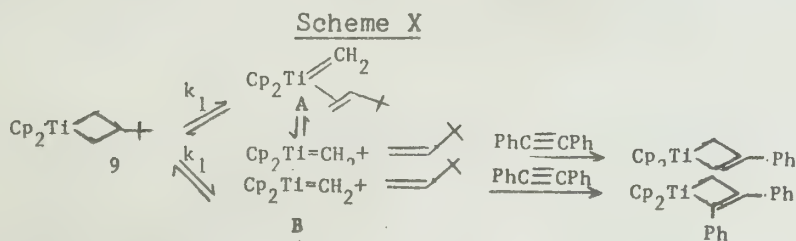


formed rapidly and subsequent addition of  $\text{AlMe}_3\text{-d}_3$  leads to exchange of the Al-Me and Ti-Me groups without any measurable isotope effect. The addition of the second equivalent of trimethylaluminum leads to the slow appearance of 1 and methane. A primary isotope effect of  $2.9 \pm 0.1:1$  was measured. In addition, kinetic data yielded the above activation parameters for the overall reaction. The primary isotope effect and the large negative entropy led Grubbs and co-workers to propose the six-membered chair transition state shown for the deprotonation of the titanium methyl by an aluminum methyl to give 1 and methane. Tebbe and co-workers have published an x-ray structure of  $\text{Cp}_2\text{TiCH}_2\text{AlCl}(\text{CH}_2\text{CMe}_3)_2$ .<sup>14</sup> Unfortunately there is disorder in the crystal between the methylene and the chloride, but the ring is planar.

### Mechanism of Methylenation

The mechanism of reaction of 1 with carbonyls should be analogous to its reaction with olefins. Grubbs and co-workers have published the metathesis kinetics of 9 with diphenylacetylene shown in Scheme X.<sup>15</sup> The reaction is first order in 9

and independent of the concentration of diphenylacetylene. The observed rate constant remains unchanged with different traps, and the addition of a small amount of 3,3-dimethyl-1-butene shows a slight rate inhibition. The enthalpy of activation for the reaction is 26.9 kcal/mol, and the entropy of activation is 8.9 eu. This data led Grubbs and co-workers to propose the mechanism is shown in Scheme X. Although A, as an intermediate, cannot be ruled out, studies using trans-9-d<sub>1</sub> indicate that the outgoing olefin exerts virtually preference for the incoming olefin.



## Synthesis of 1

Although the Tebbe reagent has shown itself to be synthetically useful, availability and cost will be important factors in determining its widespread use by synthetic chemists. The reagent may be prepared using standard vacuum line and Schlenk techniques for approximately \$225 per 100g.<sup>15,18</sup> It is also commercially available from Strem and Alfa for about \$2700 per 100g.<sup>19</sup> Cannizzo and Grubbs have reported an in-situ synthesis of **1** which works well with 4-phenylcyclohexanone and dihydrocoumarin.<sup>15</sup> Yields were only about 10% lower and a simple inert gas manifold and standard organic techniques are used.

## Summary

The Tebbe reagent has been shown to possess many advantages over the standard Wittig methylenation. It methylenates ketones in good to excellent yield without epimerization of the  $\alpha$ -position. The methylenation of esters, lactones, and amides proceeds readily, a transformation which was unsuccessful with Wittig reagents. Reaction of **1** with acid chlorides opens a facile route to methylene enolates. In addition, the Tebbe reagent provides a new route to tetrasubstituted allenes in moderate to good yield. This reactive transition metal carbene and others like it show great potential in organic synthesis.

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- (18) Using current Aldrich prices for titanocene dichloride and trimethylaluminum.
- (19) Using the current Alfa price of \$135 per 5g.



# THE BIOSYNTHESIS AND SYNTHESIS OF TYLOSIN--A 16-MEMBERED MACROLIDE ANTIBIOTIC

Reported by Raymond C. M. Lau

December 2, 1985

## Introduction

Tylosin belongs to the family of 16-membered macrolide antibiotics. Tylosin was first isolated by McGuire in 1961 from a culture of *S. fradiae*<sup>1</sup> and it was later reported to be isolated from cultures of *S. rimosus*<sup>2</sup> and *S. hygroscopicus*.<sup>3</sup> Tylosin is widely used commercially and has been shown to be very effective against pleuropneumonia-like organisms in poultry<sup>4,5</sup> and is also found to stimulate growth in animals.<sup>6</sup>

The structure of tylosin is shown in Figure 1 with the lactone ring and the sugar moieties identified.

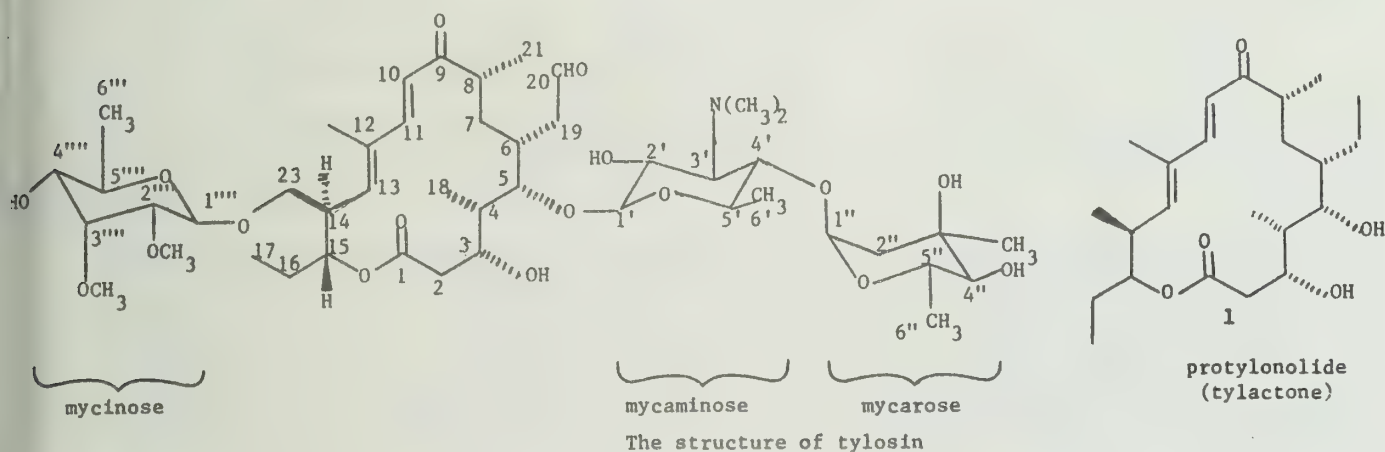


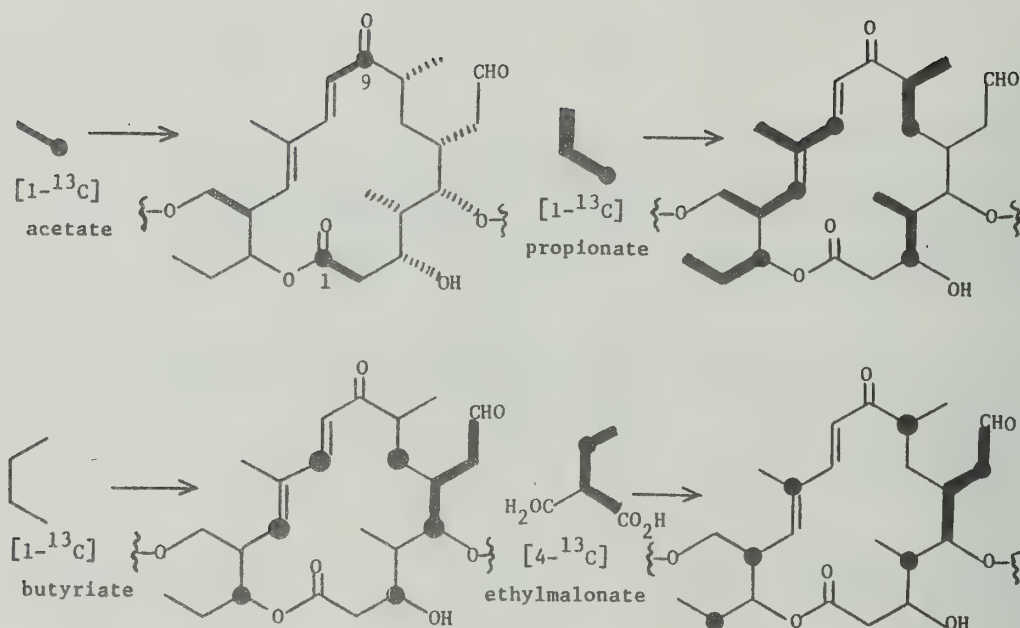
Figure 1

## Biosynthesis

Studies on other 16-membered macrolides [methymycin,<sup>7</sup> erythromycin,<sup>8</sup> leucomycin<sup>9,10</sup>] have allowed the prediction that the carbon skeleton of the lactone ring originates from acetate, propionate and butyrate. Omura et. al., confirmed this prediction by feeding C-13 labeled acetate, propionate, butyrate and ethylmalonate to *S. fradiae* and found that the lactone ring is constructed from 2 acetates, 5 propionates and 1 butyrate (Scheme I).<sup>11-15</sup>

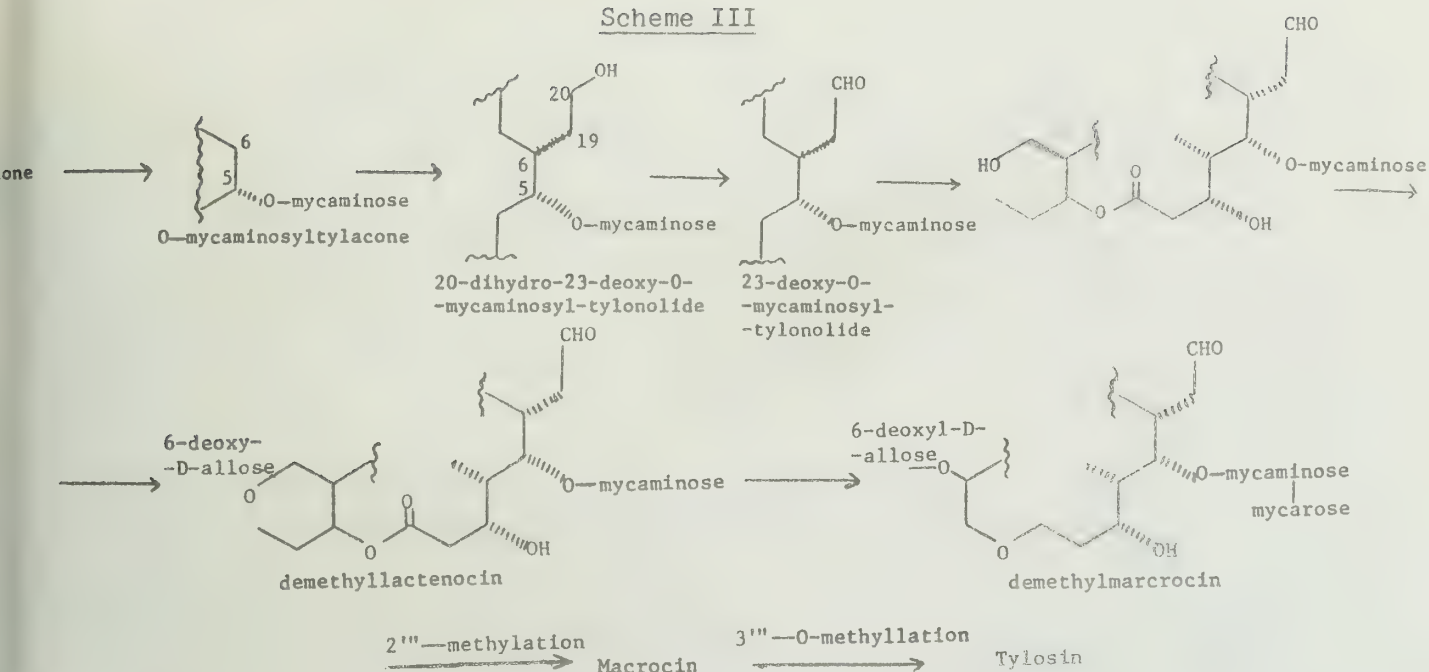
Protylonolide 1, the first non-biologically active intermediate of tylosin, was isolated by Omura et. al. from a mutant strain of *S. fradiae*.<sup>16,21</sup> Protylonolide was converted to tylosin by the parent strain (*S. fradiae* KA-427) in the presence of cerulenin, an inhibitor of fatty acid and polyketide biosynthesis, therefore establishing 1 as an intermediate of tylosin biosynthesis.<sup>17-20</sup>

Scheme I



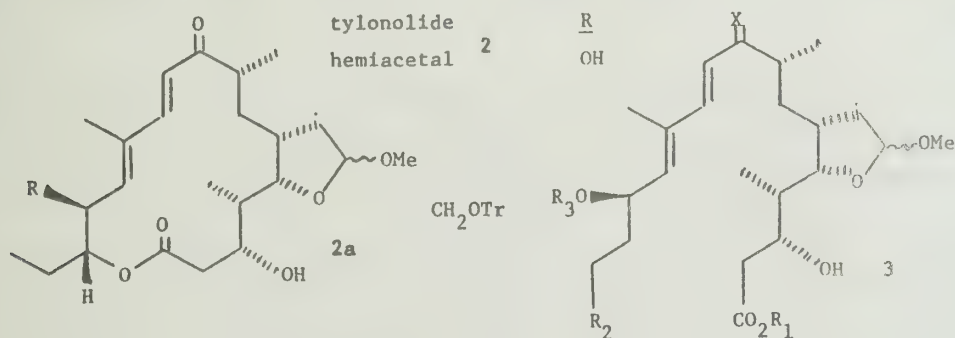
Despite the work by Omura et. al., the order of transformations from ty lactone to tylosin is still unknown. Baltz and his co-workers attempted to answer these questions by using mutants that have specific block(s) in the tylosin biosynthetic route.<sup>18,26-27</sup> From results obtained by confermenting pairs of these mutants and by feeding potential intermediates to a mutant that has a block in the biosynthesis of ty lactone, Baltz concluded that: (1) the addition of mycaminose is the first step in the conversion of ty lactone to tylosin; (2) 6-deoxy-D-allose is added to the C-23 hydroxyl methyl position of lactone before O-methylation at 2''' and 3''' position; (3) 2'''-O-methylation occurs before 3'''-O-methylation; (4) 6-deoxy-D-allose is added before mycarose; and (5) mycarose is added prior to O-methylations (Figure 1). Based upon these results, Baltz proposed a preferred biosynthetic pathway from ty lactone to tylosin (Scheme III). Similarly, Omura synthesized many derivatives of protylonolide and carried out biotransformations on *S. fradiae* KA-427 in presence of cerulenin,<sup>27</sup> and with the cell free extract of *S. fradiae*.<sup>28</sup> The results they obtained allowed Omura to propose a biosynthetic pathway which is generally in agreement with that proposed by Baltz.

Scheme III



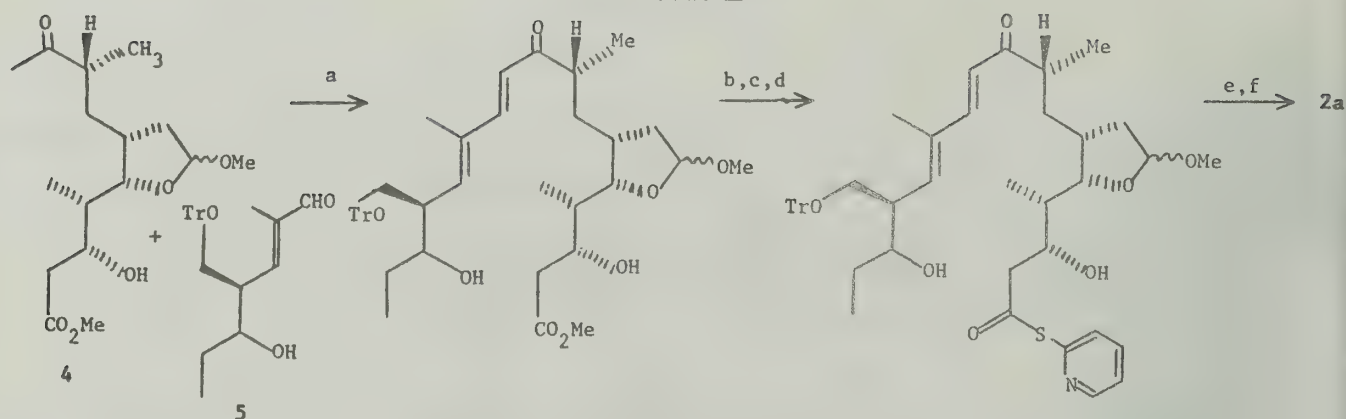
## Synthesis

Most reported total syntheses of tylosin have focused on tylonolide hemiacetal **2**, a derivative of tylactone.<sup>30,35</sup> These syntheses were all based on a similar strategy in which **2** is divided into two fragments, a C1-C9(C10) fragment, and a C11-C17 fragment. The two fragments were synthesized separately, and then joined together to form the seco acid derivative **3** and subsequently lactonized to form the ring system of **2**.



Tatsuta used glucose derivatives as his starting material for both halves. The glucose derivatives provided a stereochemically correct six carbon skeleton for the construction of both fragments 4 and 5. Final connection of 4 and 5 followed by ring closure through the 2-pyridine thiol ester 51 produced 2a (Scheme IV).<sup>30</sup>

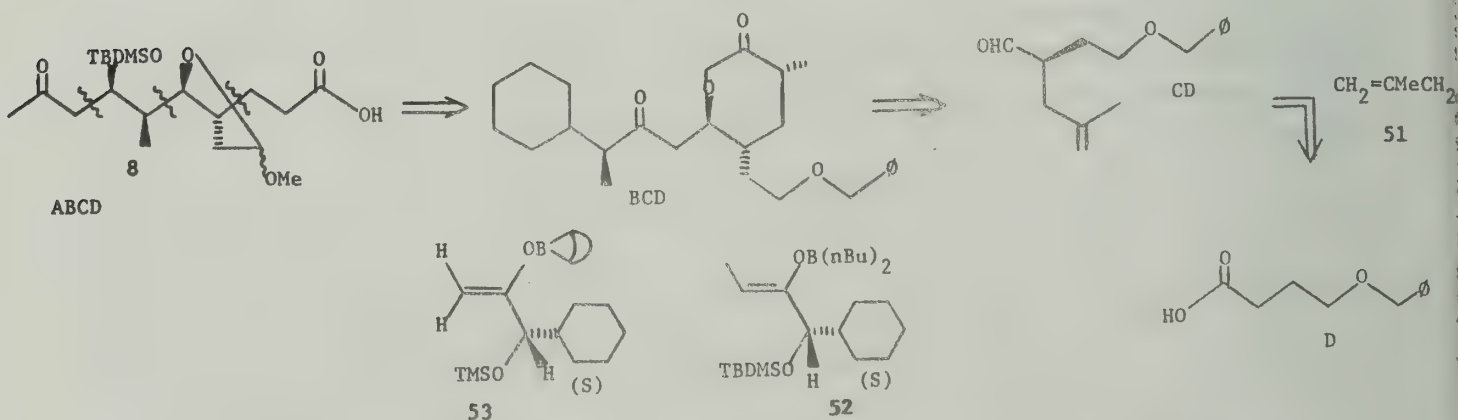
Scheme IV



Conditions: (a) LDA/THF,  $-78^{\circ} \rightarrow 0^{\circ}$ , 2h. (b)  $\text{NaBH}_4$ , MeOH,  $0^{\circ}$ . (c) 0.2N KOH/aq. MeOH,  $60^{\circ}$ , 1.5h. (d) 2,2'-dipyridyl disulfide,  $\text{Ph}_3\text{P}$ ,  $20^{\circ}$ . (e) PhMe,  $110^{\circ}$ , 2h. (f)  $\text{CrO}_3$ /HMPT,  $20^{\circ}$ , 20h.

Masamune<sup>31</sup> developed a convergent synthetic scheme for the synthesis of the C1-C9 fragment 8. Starting with 4-benzyloxybutyric acid 9,<sup>39</sup> 8 was built up gradually with acetate or propionate synthetic equivalents 51, 52, 53 (Scheme V).

Scheme V



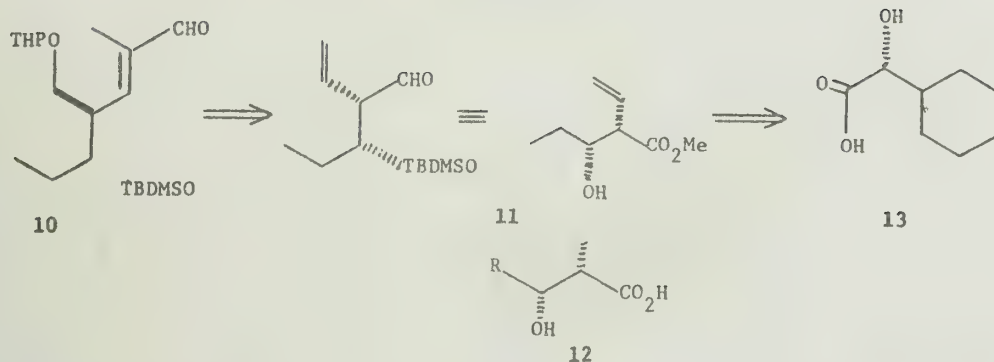
The key reaction in this synthetic scheme was the formation of fragment BCD from CD. The CD fragment was synthesized as a racemic mixture. Addition of 52 to CD resulted in the exclusive formation of one product from each epimer with more than 50 to 1 diastereoselection.

The pathway to the C11-C17 fragment 10 started with R-hydroxymandelic acid 13 and through intermediate 11, a derivative of 12 which is a fundamental structural unit embedded in numerous natural products of propionate origin (Scheme VI).<sup>39</sup>

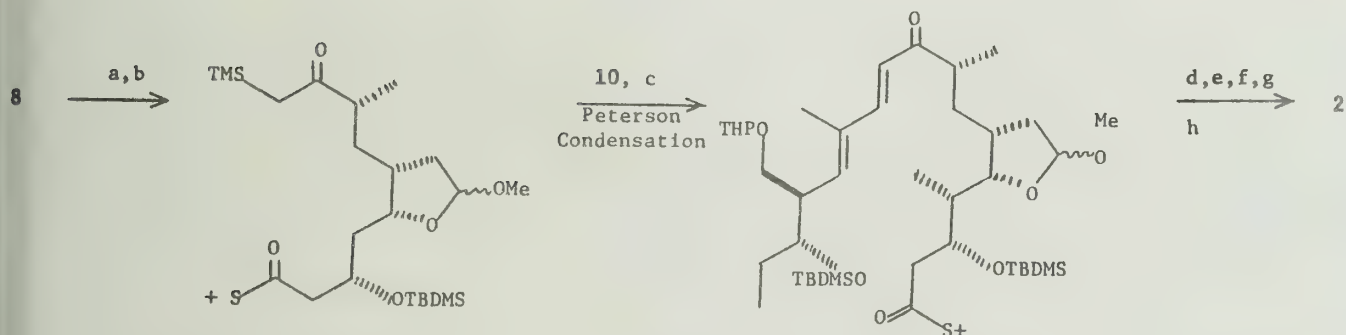
Connection of 8 and 10 through Peterson condensation and final ring closure with dibenzylphosphoryl chloride produced 2 with an overall yield of 0.2% (Scheme VII).



Scheme VI



Scheme VII

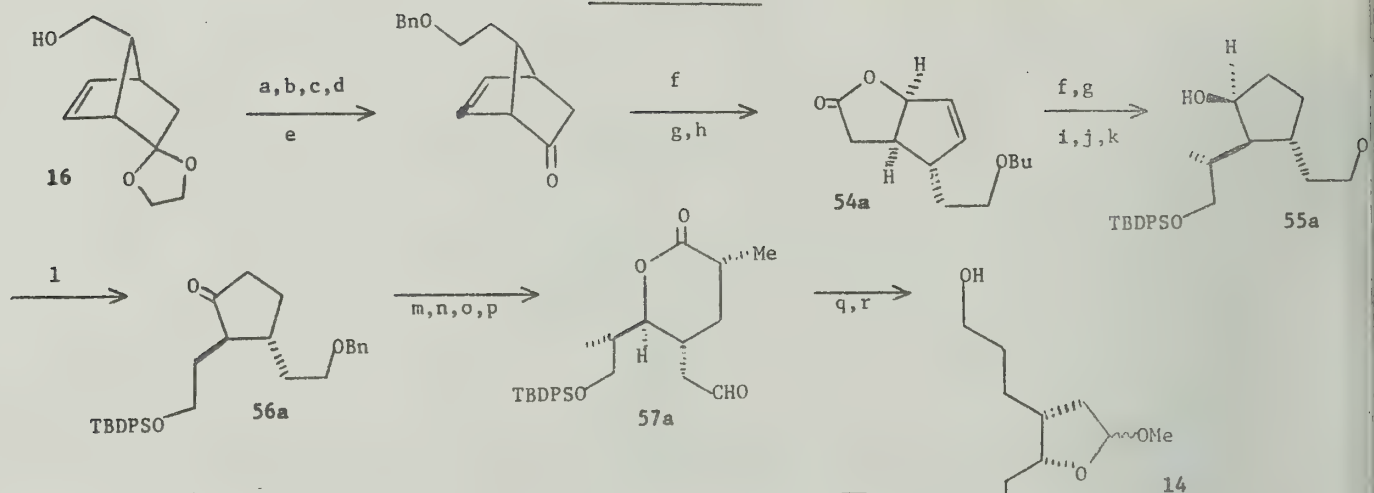


Conditions: (a) 2,2'-dipyridyl disulfide,  $\text{Ph}_3\text{P}$ ,  $\text{PhH}$ , RT, 2.5h. (b)  $\text{LiCu}(\text{TMSCH}_2)_2$ ,  $\text{Et}_2\text{O}$ ,  $-78^\circ$ , 15 min. (c)  $\text{nBuLi}$ ,  $(\text{Me}_3\text{S})_2\text{NH}$ ,  $\text{THF}$ ,  $-78^\circ$ , 1h. (d)  $(\text{CF}_3\text{CO}_2)_2\text{Hg}$ ,  $\text{NaHPO}_4$ ,  $\text{CH}_2\text{Cl}_2$ , RT, 1h. (e)  $\text{HF/pyr.}$ ,  $\text{THF}$ , RT, 40h. (f)  $(\text{PhO})_2\text{POCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{THF}$ ,  $0^\circ$ , 30 min. (g) DMAP,  $\text{PhH}$ ,  $80^\circ$ , 18h. (h) 70%  $\text{AcOH}$ ,  $85^\circ$ , 1h.

Grieco used a common starting material, 16, for both fragments.

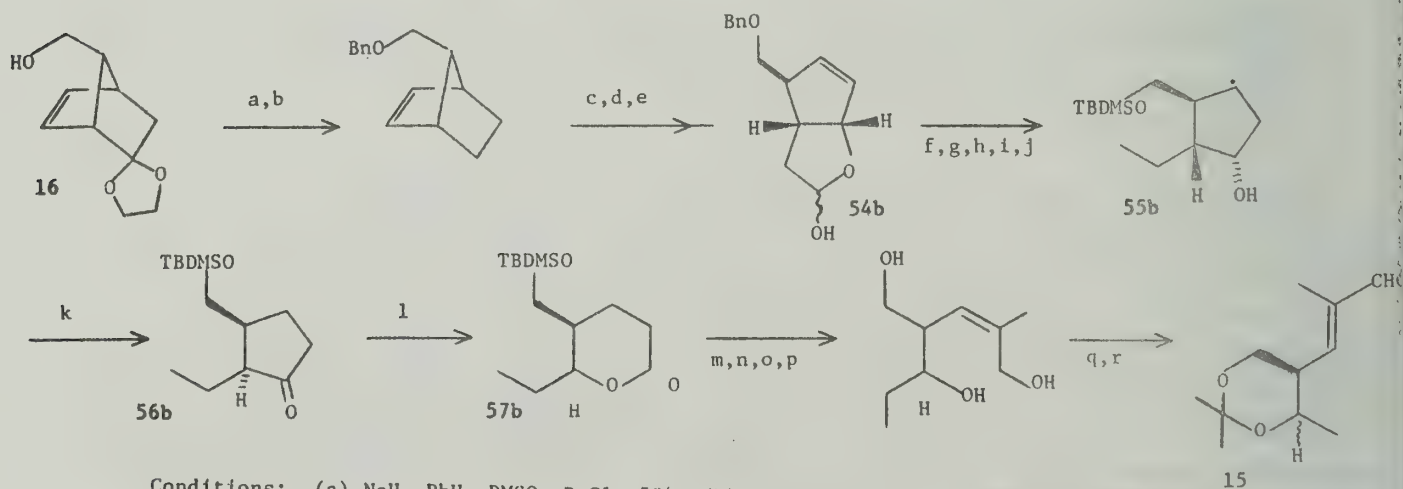
Bicyclo[2.2.1]heptenol 16 is readily available from nonbornadiene. Not only did both fragments (14 and 15) have the same starting compound, their synthetic pathways from 16 were also quite similar. The bicycloheptenol was reduced ( $\text{LAH}$ ;  $\text{NaBH}_4$ ,  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ ) to a cyclopentanol 55a,b through a bicycloactol 54a,b. The necessary substituent groups were added and the hydroxyl group was oxidized to form a cyclopentanone 56a,b. Baeyer-Villiger oxidation resulted in the formation of a six-membered lactone 57a,b. Subsequent opening of the lactone afforded 14 or 15 (Scheme VIII, IX).<sup>40</sup>

## Scheme VIII



Conditions: (a) TsCl, pyr. (b) NaCN, DMSO, 100°. (c) 40% aq. KOH, HOCH<sub>2</sub>CH<sub>2</sub>OH, 130°. (d) LAH, THF. (e) NaH, PhH, DMSO, BnCl, 50°, 10% HCl, THF. (f) LDA, THF, -78°, MeI. (g) 30% H<sub>2</sub>O<sub>2</sub>, 10% NaOH, MeOH/THF/H<sub>2</sub>O (1:1:1), -5°. (h) BF<sub>3</sub>·Et<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>. (i) LAH, Et<sub>2</sub>O, 0°. (j) NaBH<sub>4</sub>, NiCl<sub>2</sub>·6H<sub>2</sub>O, 0°. (k) TBDPSiCl, CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>N, DMAP, 0°. (l) CrO<sub>3</sub>, 2 pyr., CH<sub>2</sub>Cl<sub>2</sub>, 0° (10 min.) → 25° (~30 min.). (m) MCPBA, CH<sub>2</sub>Cl<sub>2</sub>, NaHCO<sub>3</sub>, [(Me)<sub>3</sub>CC<sub>6</sub>H<sub>2</sub>(Me)OH]<sub>2</sub>SO. (n) LDA, THF, -78°C, MeI, -78°C → -40°. (o) H<sub>2</sub>, Pd-C, EtOH. (p) CrO<sub>3</sub>, pyr., CH<sub>2</sub>Cl<sub>2</sub>. (q) TsOH, MeOH. (r) LAH, Et<sub>2</sub>O, 0°.

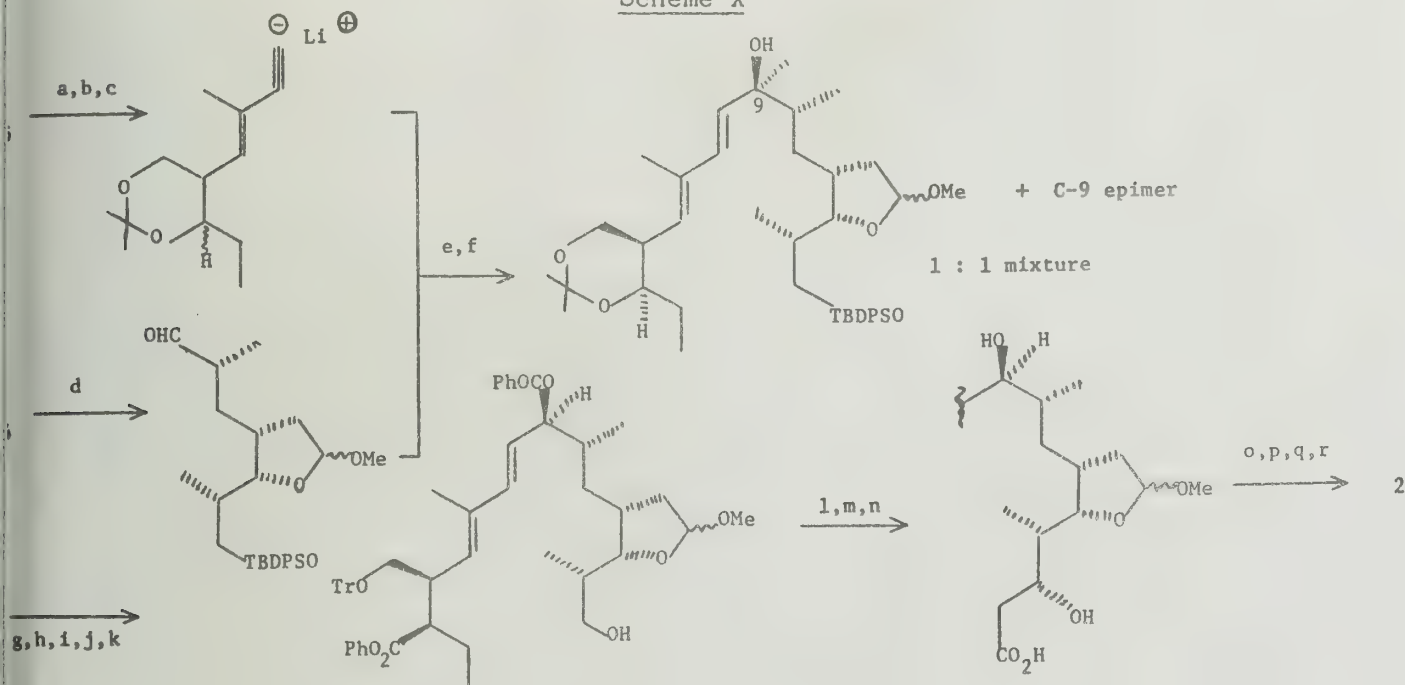
## Scheme IX



Conditions: (a) NaH, PhH, DMSO, BnCl, 50°. (b) 10% HCl, THF. (c) 30% H<sub>2</sub>O<sub>2</sub>, 10% NaOH, MeOH/THF/H<sub>2</sub>O (1:1:1), -5°. (d) BF<sub>3</sub>·Et<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>. (e) LAH, Et<sub>2</sub>O, 0°. (f) NaBH<sub>4</sub>, NiCl<sub>2</sub>·6H<sub>2</sub>O, MeOH, 0°. (g) PhSeCN, Bu<sub>3</sub>P, THF, -23°. (h) Bu<sub>3</sub>SnH, PhMe, AIBN, 105°. (i) H<sub>2</sub>, 10% Pd/C, EtOAc. (j) TBDMSCl, imidazole, DMF. (k) CrO<sub>3</sub>, 2 pyr., CH<sub>2</sub>Cl<sub>2</sub>, 0°. (l) MCPBA, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0°. (m) LDA, THF, -78°, MeI. (n) LDA, THF, -78°, PhSeCl. (o) 30% H<sub>2</sub>O<sub>2</sub>, THF, 0°. (p) LiAlH(OMe)<sub>3</sub>, THF, 0°. (q) BuLi, THF, P-MeC<sub>6</sub>H<sub>4</sub>SCl, SiO<sub>2</sub>. (r) [o].

Transformation of 14 and 15 to their corresponding lithium reagent and aldehyde allowed effective combination to the seco acid derivative. Final ring closure through the 2-pyridinethiol ester, followed by oxidation resulted in 2 with an overall yield of 0.019% (Scheme XII).

Scheme X



**Conditions:** (a)  $\text{Ph}_3\text{P}$ ,  $\text{CBr}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{Na}_2\text{CO}_3$ . (b) acetone, CSA,  $\text{CuSO}_4$ . (c)  $\text{BuLi}$ , THF,  $-78^\circ$ . (d)  $\text{CrO}_3$ , 2 pyr.,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ$ , 1h. (e)  $\text{Et}_2\text{O}$ ,  $0^\circ$ . (f) LAH, THF,  $5^\circ$ . (g)  $\text{PhCOCl}$ , DMAP. (h) PPTS, MeOH. (i)  $\text{TrCl}$ ,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ . (j)  $\text{PhCOCl}$ , Pyr., DMAP. (k)  $\text{Bu}_4\text{NF}$ , THF. (l)  $\text{CrO}_3 \cdot 2 \text{ pyr.}$ ,  $0^\circ$ . (m)  $\text{LiCH}_2\text{CO}_2\text{Me}$ , THF,  $-78^\circ$ . (n)  $\text{NaOCH}_3$ , MeOH. (o)  $\text{INNaOH/MeOH}$  (1:4),  $60^\circ$ , 2h. (p) 2,2'-dipyridyl disulfide  $\text{Ph}_3\text{P}$ ,  $\text{PhMe}$ , 24h. (q)  $\text{MnO}_2$ ,  $\text{CH}_2\text{Cl}_2$ , 3h. (r)  $\text{H}_2\text{O/AcOH/THF}$  (1:1:3).

## Summary

Studies that led us to the elucidation of the origin of the lactone ring of tylosin, and the biosynthesis pathway from tylactone to tylosin were discussed. The lactone ring originated from 2 acetate, 5 propionate and 1 butyrate. The biosynthetic pathway involving the addition of mycaminose to tylactone as the first step, subsequent oxidation at C-20 and C-23 position, addition of 6-deoxy-D- allose followed by mycarose and finally O-methylations, is the preferred scheme from tylactone to tylosin.

Three total syntheses of tylosin hemiacetal have also been reported. Among them, the synthetic approach by Masamune was accomplished with relatively high dia-stereoselectivity and the highest yield (0.2%).

For the synthesis of the two individual fragments, the scheme by Masamune for the synthesis of the C11-C17 fragment is clearly superior than the other two (21.2% vs. 10%, 12%), while the synthetic scheme of Grieco on the C1-C9 fragment is more desirable (13%).

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ORGANIC SEMINAR ABSTRACTS

1985-86, Spring Semester

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# $\eta^4$ -1,3-DIENE AND $\eta^5$ -DIENYLIRON COMPLEXES IN ORGANIC SYNTHESSES

Reported by Zhiguo Song

January 23, 1986

$\eta^4$ -1,3-Dieneiron complexes have been known for three decades.<sup>1a</sup> However, synthetic uses for these complexes have only been developed in the past ten years. Much of the pionerring work was done by Birch<sup>2</sup> and coworkers and more recently by Pearson and coworkers.<sup>1</sup> Because the older work has been reviewed,<sup>1c</sup> this seminar covers developments occuring in the last five years.

## Basic Structural Features and Physical Properties

$\eta^4$ -1,3-Dieneiron (1) and  $\eta^5$ -1,3-dienyliron (2), are represented in Figure 1, where L's symbolize two-electron ligands and the diene can be cyclic or acyclic.  $\eta^5$ -cyclopentadienyliron (ferrocene) complexes will be excluded from this seminar. The most commonly used complexes are tricarbonyl-1,3-cyclohexadiene and dienyliron where  $X^- = PF_6^-$  or  $BF_4^-$ . These complexes are usually air sensitive, not sensitive to water, readily recrystallizeable and can be characterized by conventional methods, such as MS, <sup>1</sup>HNMR, <sup>13</sup>C NMR, IR, UV, and x-ray crystallography. The most important spectroscopic properties of the tricarbonylcyclohexadiene and dienyl iron complexes have recently been reviewed by Birch.<sup>2</sup>

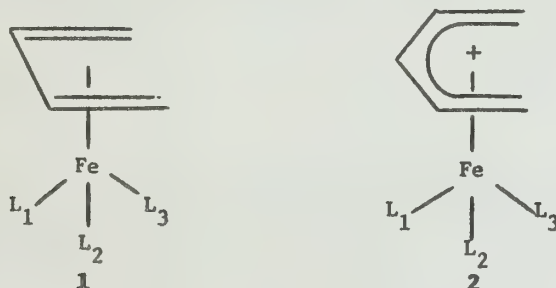
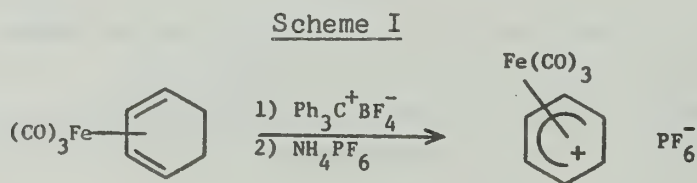


Figure 1

## Preparation<sup>1-9</sup> and Demetallation

Tricarbonyldieneiron complexes are prepared by 1,3-diene ligand displacement from  $Fe(CO)_5$ ,  $Fe_2(CO)_9$ , or other " $Fe(CO)_3$ " transfer complexes.<sup>3d,5</sup> Other ligands such as  $PR_3$  can be introduced by ligand displacement from the tricarbonyl complexes.<sup>3c</sup> The  $\eta^5$ -dieneyliron complex can be prepared by hydride abstraction from the diene complex<sup>1,2,6</sup> or protonation of 1,3,5-triene<sup>4b,9</sup> ligand. Alternatively, the allylic OR or  $NR_2$  ( $R=H$ , alkyl, etc.) group may be removed under acidic conditions.<sup>3a,3b,8,9</sup> The most used reagent for hydride abstraction is  $Ph_3C^+BF_4^-$ . Acids like  $H_2SO_4$ ,  $HBF_4$ ,  $HPF_6$  and

$\text{CF}_3\text{CO}_2\text{H}$  have also been used for hydride abstraction and protonation.<sup>5,9</sup> Oxidation of the diene complex by  $\text{Tl(III)}$  was reported for preparation of certain regiospecific  $\eta^5$ -cyclohexadienyliron complexes.<sup>18d,19</sup> Scheme I shows one example of preparation of a dienyliron complex.



Birch has recently reviewed the regioselectivity of hydride abstraction from some cyclohexadieneiron complexes.<sup>2</sup>

In order to resolve chiral diene or dienyliron complexes, additional chiral centers have been reversibly introduced into the complex by two general methods: (a) addition of a chiral nucleophile to the dienyl ligand;<sup>3e,4a,4b,8a,8b</sup> and (b) derivatizations of side chain functional groups.<sup>1c</sup> Other enantiomeric preparations involve use of chiral  $\text{Fe(CO)}_3$  transfer reagents.<sup>3d</sup> Optically active diene or dienyliron complexes can be used in asymmetric syntheses.

Demetallation of the diene complex is required when free ligand is desired. The usual method is to oxidize the metal with mild oxidants,  $\text{Me}_3\text{NO}$  being one of the best.  $\text{Fe(III)}$ ,  $\text{Ce(IV)}$  and some other reagents have been used also.<sup>1,2</sup>

## General Reactions

### I. $\eta^4$ -Dieneiron Complexes.

(a) Diene protection<sup>10</sup>: Because of the stability of the dieneiron complex, a conjugated diene can be protected against most standard organic manipulations. This type of protection is especially useful when one needs to discriminate a conjugated diene system from an isolated double bond. Scheme II illustrates such an example.<sup>10b</sup>

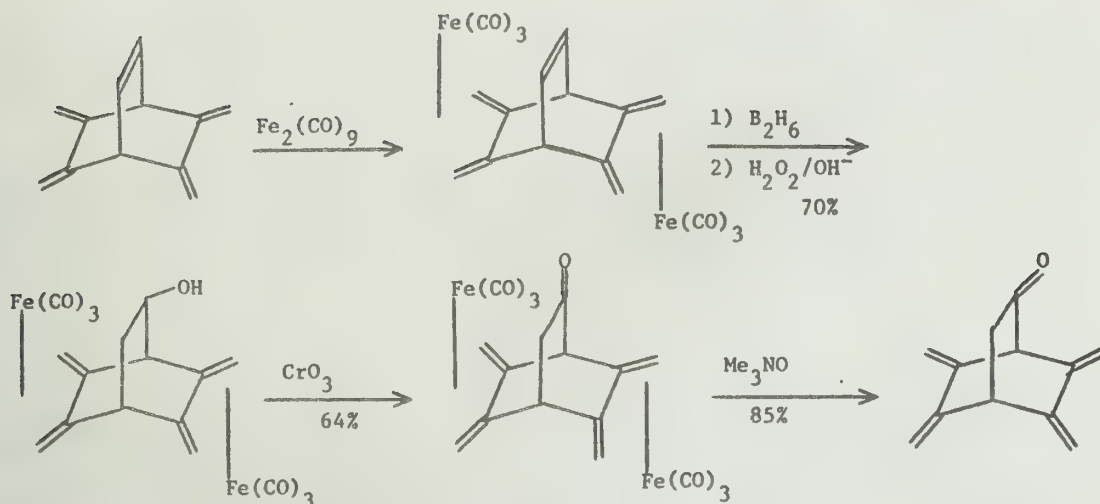
(b) Diene regeneration: The diene ligand can be regenerated by dissociation of the complex for subsequent reactions such as Diels-Alder reactions or electrocyclic reactions.<sup>11</sup>

(c) Remote stereochemical control: Due to its chirality, the diene complex can be used for diastereoselective or enantioselective control in organic synthesis.<sup>12</sup>

(d) Promotion of ligand oligomerization:<sup>13,14</sup>

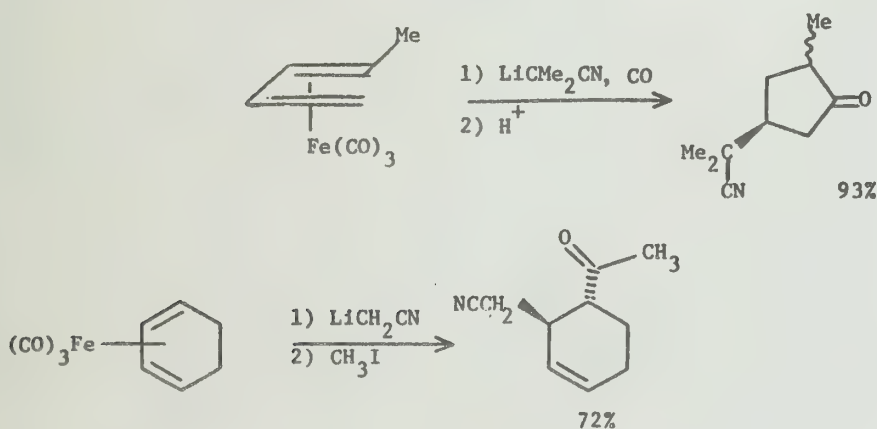


Scheme II



(e) Nucleophilic addition: The diene in the tricarbonyl diene complex can undergo reaction with nucleophiles. Semmelhack's recent work on the reaction of lithium reagents with these complexes serves as an example (Scheme III).<sup>16</sup>

Scheme III



(f) Friedel-Craft reactions.<sup>15</sup>

## II. $\eta^5$ -Dienyliron Complex.

1. Cyclohexadienyl complexes. Nucleophilic addition to the dienyl ligand has been the subject of extensive research and it is central to the interests of organic chemists.<sup>1,2,17-22</sup> The nucleophiles so far investigated include alcohols, amines, phosphines, halides and analogues, organometallic reagents (Li, Cu, Zn, Cd, Si, Sn, Pb, Ge, etc.) enolates, activated aromatics, etc. While the stereochemistry of the nucleophilic addition has been found to be almost exclusively "exo" to the metal moiety, most research has focused on regiochemistry.

Depending on the original substitution pattern of the cyclohexadiene and the subsequent manipulations, one can get a large variety of electrophilic synthetic equivalents of cyclohexane or aromatic derivatives.<sup>17-22</sup> The following is a list of some of the most important ones.

Complexes	Synthons	Examples	References
[M = Fe(CO) <sub>3</sub> , R = Me, H]			
			17a 18,21,22
R' = Alkyl, etc.			
			18e
			17b,c
			17c

2. Other dienyl systems. Open chain dienyliron complexes have been investigated to but a slight extent. Although a relatively general method for preparation of these complexes has been developed, very few nucleophilic addition reactions have been reported.<sup>2c,9</sup> For the dicarbonyltriphenylphosphinecycloheptadienyliron complex, clean nucleophilic addition has been reported for a variety of carbon nucleophiles.<sup>23</sup>  $\eta^5$ -1,3-Cyclooctadienyliron complex has received little attention.<sup>7</sup> Presumably, in larger ring systems, nucleophilic addition tends to give multiple products.

### Applications in Natural Product Syntheses

So far, synthetic routes using  $\eta^4$ -diene and  $\eta^5$ -dienyliron complex intermediates for the preparation of several types of natural products have been investigated. These include steroids,<sup>24c,25</sup> histrionotoxin congeners,<sup>24b</sup> terpenes,<sup>24a</sup> alkaloids,<sup>11,18e</sup> and even amino acid.<sup>17b</sup> Recent success in the preparation of these synthetic intermediates include those for pyrethroids,<sup>12a,b</sup> deplancheine,<sup>11</sup> perhydrohistrionicotoxin,<sup>24b</sup> limaspermine,<sup>24c</sup> gabaculine,<sup>17b</sup> o-methyljoubertiamine,<sup>18e</sup> carvone<sup>19</sup> and sylvecarvone.<sup>19</sup> Most of them employed  $(2\text{-MeO-}\eta^5\text{-1,3-cyclohexadienyl})\text{Fe}(\text{CO})_3^+$  as the synthetic equivalent of 4-cationic-2-cyclohexenone.

### Theoretical and Mechanistic Studies

From the structural and mechanistic point of view, there are several general problems to be answered. One concerns the stereochemistry of the hydride abstraction and of nucleophilic addition. Why do these reactions occur almost exclusively "exo" to the metal face in the cyclohexadienyl case? No doubt, it is the steric hinderance created by the metal moiety that plays the dominant role. The second question concerns the regioselectivity observed for hydride abstraction and for the nucleophilic addition reactions. While regioselectivity of the first has been qualitatively rationalized based on extended Hukel MO<sup>27</sup> and INDO<sup>20b</sup> calculations, the regioselectivity of the second must depend upon the mechanisms of nucleophilic addition which brings us to the third general question concerning organoiron chemistry. So far, systematic investigation of the kinetics of these reactions is relatively rare, especially for the addition of carbon nucleophiles. First mechanistic question is which site is attacked by the nucleophile, CO, metal, or the ring? Work done by Brown and coworkers<sup>28,32</sup> shows that for tricarbonyl- $\eta^5$ -1,3-cycloheptadienyliron, hard nucleophiles may attack the carbonyl or metal (e.g.  $\text{EtO}^-$  was shown to attack CO at low temperature), soft nucleophiles such as phosphines tend to attack the dienyl ligand in polar solvents. Systematic investigation on the addition of a series of aromatic phosphines and phosphites to  $\text{C}_6\text{H}_7\text{Fe}^+(\text{CO})_3$  reveals that there is not much

positive charge buildup in the transition state of the rate limiting step.<sup>30</sup> Kinetic investigation carried out by Kane-Maguire and coworkers<sup>30</sup> on the reaction of  $(\eta^5\text{-cyclohexadienyl})\text{Fe}(\text{CO})_3^+$  with  $\text{Me}_3\text{MAr}$  (M=Si, Ge, Sn, Pb) led them to postulate an intermediate. Observations reported by Kane-Maguire<sup>29</sup> and Pearson<sup>31</sup> suggest tht the counteraction of the nucleophile may also play an important role in the addition to  $(\eta^5\text{-2-MeO-C}_6\text{H}_6)\text{Fe}^+$ .

From the development of the chemistry of  $\eta^4\text{-1,3-dieneiron}$  and  $\eta^5\text{-1,3-dienyliron}$  complex in recent years, it should be seen that this very promising area awaits further exploration. More mechanistic work is needed and rapid development is expected.

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# $\beta$ -LACTAMASE INHIBITION TO OVERCOME PENICILLIN RESISTANCE

Reported by Du-Jong Baek

January 27, 1986

Since Fleming discovered penicillin in 1928,<sup>1</sup> thousands of  $\beta$ -lactams have been developed for the treatment of bacterial infections. The potency of a  $\beta$ -lactam antibiotic is largely controlled by its ability to inhibit the transpeptidase enzyme required in the last stage of the biosynthesis of the cell wall, leading to cell death.<sup>2</sup> However, the emergence of resistant strains of pathogenic microorganisms induced by the increased use of  $\beta$ -lactams threatened their efficacy as antibiotics. The most common type of resistance is the appearance of  $\beta$ -lactamase which is produced by bacteria in their own defense and catalyzes the hydrolytic destruction of the antibiotic in the periplasm before it can reach the target enzyme (Figure 1).<sup>3</sup>

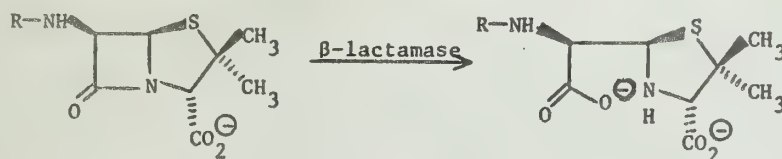
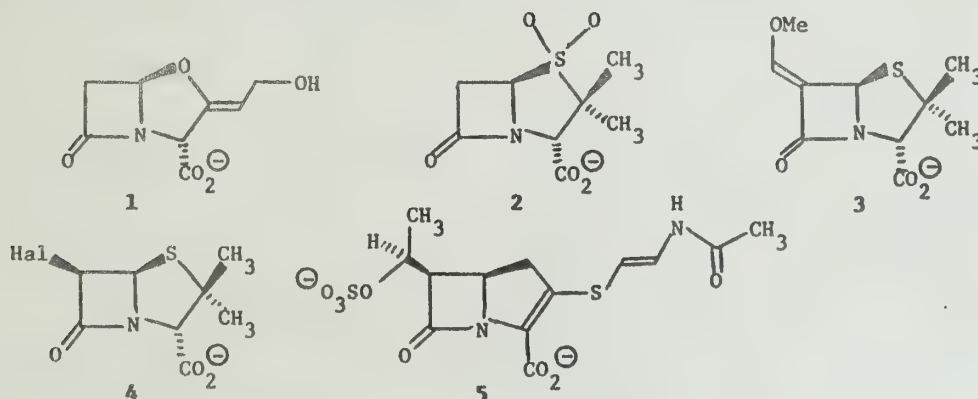


Figure 1

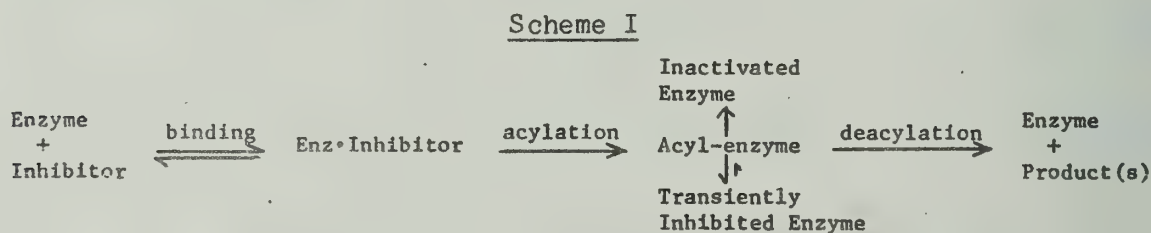
In order to overcome the destructive action of the  $\beta$ -lactamase, two approaches have been adopted. The first is modification of the structure of the  $\beta$ -lactam to make it insensitive to hydrolysis by the  $\beta$ -lactamase. However, it seems almost inevitable that after extensive use, resistant bacteria will arise and the endless battle will continue. In an attempt to overcome this, a second approach is more promising; the use of a reagent that inactivates the  $\beta$ -lactamase, in synergy with a  $\beta$ -lactam antibiotic.

Since the discovery of clavulanic acid (1) in 1976,<sup>4</sup> a number of other reagents having powerful inhibitory properties toward  $\beta$ -lactamases have been reported. Some examples are compounds 2 to 5. Mechanistic investigation of the interaction has shown that they are all "suicide" or "mechanism-based"



inhibitors, in the sense that they are destroyed by the  $\beta$ -lactamase, but tethered permanently (or for a sufficiently long time) in the active site to prevent the  $\beta$ -lactamase from further hydrolysis of other  $\beta$ -lactams.

When the inhibitor is added to the enzyme and the remaining catalytic activity is followed with time, three distinct processes can be discerned after acylation of the enzyme (on a serine hydroxyl group by the  $\beta$ -lactam),<sup>5</sup> according to the kinetic pathways shown in Scheme I. Those include deacylation (turnover to free enzyme), transient inhibition and permanent inactivation.



While there can be irreversible inactivation by transimination of an enzyme lysine residue in 2,<sup>6</sup> by nucleophilic attack of the lysine residue in 3,<sup>7</sup> or by formation of a stable dihydrothiazine unit in 4,<sup>8</sup> there is only transient (reversible) inhibition in 5.<sup>9</sup> However, the enzyme is preoccupied long enough to allow the antibiotic to reach its target.

Since both transpeptidase and  $\beta$ -lactamase have similar functionality, a reagent that acylates both types of enzyme but does not deacylate would be a very potent antibiotic owing to simultaneous inactivation of the  $\beta$ -lactamase and inhibition of cell-wall synthesis catalyzed by transpeptidase.

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# SPIROKETALS, IMPORTANT SUBUNITS IN NATURAL PRODUCTS

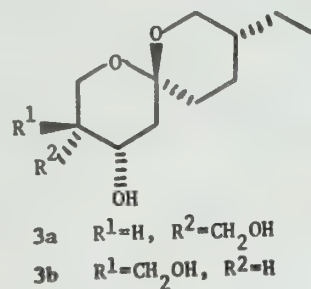
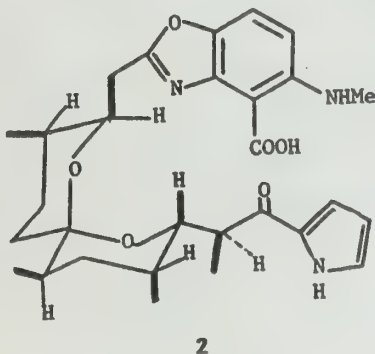
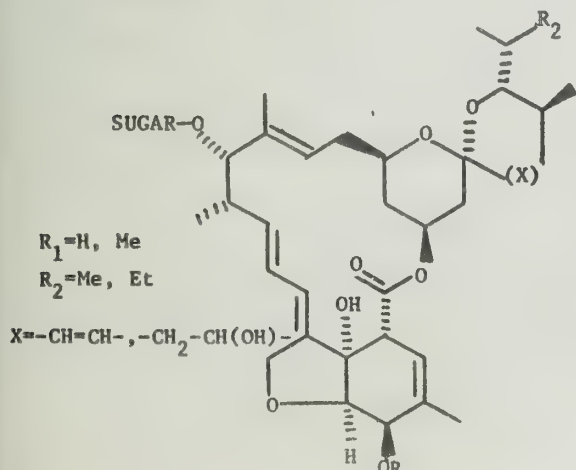
Reported by Gary A. Hite

January 30, 1986

Spiroketal, particularly substituted 1,7-dioxaspiro[5.5]undecanes, occur as subunits in many natural products. The avermectins,<sup>1</sup> 1 are a group of fermentation products from Streptomyces avermitilis which exhibit potent anthelmintic and insecticidal activities by interference with neurotransmission.<sup>2</sup> Ivermectin, the 22,23-dihydro derivative of avermectin B<sub>1a</sub>, is a commercial antiparasitic agent for treatment of livestock.<sup>3</sup> These compounds contain a spiroketal moiety as part of a 16-membered macrolide ring along with a glycosidic linkage. The structurally similar milbemycins<sup>4</sup> are a family of antibiotics from Streptomyces B-41-146, which possess potent pesticidal properties against a variety of pests but lack phytotoxicity.<sup>5</sup> Antibiotic A-23187 (calcimycin),<sup>6</sup> 2, isolated from cultures of Streptomyces chartreusensis, is an ionophore capable of transporting divalent cations (esp. Ca<sup>2+</sup>) through lipid membranes. The structurally simple spiroketals, Talaromycin A and B, 3a and 3b,<sup>7</sup> are avian toxins produced by the fungus Talaromyces stipitatus. These toxins are able to block outward potassium fluxes, leading to muscle dysfunction in mammals.

Spiroketal also exhibit a special stereoelectronic property known as the anomeric effect.<sup>8</sup> Explained as electronic delocalization due to overlap of an oxygen lone pair with the sigma antibonding orbital of an antiperiplanar C-O bond, the magnitude of this effect has been determined to be at least 1.4 kcal/mol for this system.<sup>9</sup> As a result of this stabilization as well as minimization of steric effects, the thermodynamically most stable conformation of 1,7-dioxaspiro[5.5]undecane has been shown to be 4 where each oxygen atom is situated axial to the opposite ring.

For these two reasons, spiroketals have received much attention in synthetic model studies<sup>10</sup> as well as total syntheses<sup>11</sup> of the aforementioned natural products. The different synthetic strategies for constructing 1,7-dioxaspiro[5.5]undecanes are therefore worthy of review.



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# RECENT APPLICATIONS OF FLASH VACUUM THERMOLYSIS: THE RETRO DIELS-ALDER REACTION

Reported by James Gruber.

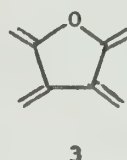
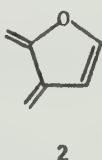
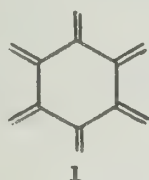
February 3, 1986

Reactions conducted at high temperature and low pressure are becoming increasingly used to produce unusual organic molecules. Flash Vacuum Thermolysis (FVT), as the technique has come to be called, has many synthetic applications. The subject has been reviewed.<sup>1</sup>

FVT techniques have been often used to promote retro Diels-Alder reactions to sometimes generate unusual and/or highly energetic compounds and intermediates.<sup>2</sup>

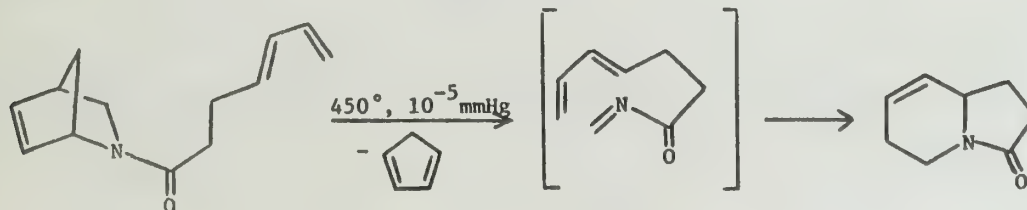
The use of FVT and retro Diels-Alder reactions has developed into two interesting categories. By this approach, one may form compounds of unusually high energy and/or reactivity which cannot be formed by more conventional synthetic methods. One may also use Diels-Alder adducts as masks for olefinic bonds in a synthetic strategy.

In the first category, Ripoll and his associates have made major efforts to use FVT and retro Diels-Alder reactions to unmask allenes,<sup>3</sup> ethendiols,<sup>4</sup> trienes and pentatetraenes,<sup>5</sup> 2-aza-1,3-dienes,<sup>6</sup> and N-acylimines.<sup>7</sup> Intriguingly, workers have succeeded in forming such unusual structures as hexaradialene, **1**,<sup>8</sup> 2,3-dihydro-2,3-bis(methylene)-furan, **2**,<sup>9</sup> and tetramethylene-tetrahydrofuran, **3**.<sup>10</sup>



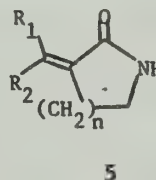
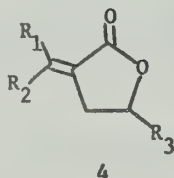
The practicality of the Diels-Alder adduct as a temporary mask for a olefinic bond has been exploited also. Zwaenburg and others have investigated the use of FVT and retro Diels-Alder reactions to form cyclopentadienone epoxides and other cyclopentenoid structures.<sup>11</sup> Ripoll has used these techniques in the synthesis of an intermediate to  $\delta$ -coniceine, an idolizidine alkaloid (Scheme I).<sup>7</sup>

Scheme I





Several groups have investigated the formation of  $\alpha$ -methylene- $\gamma$ -butyrolactones, 4, by FVT.<sup>12</sup> Compounds of this general type may be of some interest as anti-tumor agents. We have recently prepared some  $\alpha$ -methylene- $\gamma$ -butyrolactams, 5, by FVT. Similar compounds have been synthesized recently via a lengthy sequence.<sup>13</sup> Such  $\alpha$ -methylene- $\gamma$ -butyrolactams as have been biologically evaluated have displayed interesting properties.



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## RECOGNITION OF ORGANIC MOLECULES USING IMPRINTED POLYMERS

Reported by Linda T. Pilla

February 10, 1986

Synthesis of imprinted polymers having three dimensional cavities is an attempt to mimic cavities of enzymes. This abstract deals with the process of imprinting polymers and their potential for "memory" of molecular shape and functionality. A review of this material is anticipated.<sup>1</sup>

The process of imprinting polymers, also termed template or host-guest polymerization, involves connecting a template to a polymerizable material, polymerizing under conditions affording extensive crosslinking, and removing the template without destroying the three dimensional structure of the polymer. The interactions between template and polymerizable material need to be strong enough to survive the polymerization process but sufficiently reversible to allow the template to be freed from the polymer. Templates have been held in place as imines, boronic esters, and ketals, or by coulombic, hydrogen bonding,  $\pi$ - $\pi$ , steric, van der Waals, hydrophobic and dipole-dipole interactions. Through competition studies, chromatography, and synthesis, such cavities have been shown to have a specific affinity for the template molecule.<sup>1</sup>

A number of enantiomerically pure compounds have been used as templates for imprinting polymers. The resulting polymers show selectivity for the enantiomer used in imprinting. Compounds used as templates have been single enantiomers of t-boc-proline,<sup>2</sup> phenyl alanine and derivatives,<sup>3,4</sup> N-benzylvaline,<sup>5</sup> mannoside and derivatives,<sup>6</sup> mannitol,<sup>7,8</sup> propanediol,<sup>8</sup> glyceric acid and derivatives,<sup>9</sup> and mandelic acid.<sup>10</sup> The highest selectivity reported is obtained by mannitol where a separability factor,  $\alpha$ , of 3.66 is observed<sup>7,8</sup> and by N-benzylvaline where the polymer incorporated essentially only one enantiomer (ee of 99.0%).<sup>5</sup>

Polymers selective for the distance between the carbonyls of diketones and dialdehydes have been developed. Polymers prepared by Shea et. al. are able to distinguish between diketones. For the best case, separation of 1,3-diacetylbenzene and 2,7-diacetylfluorene, a separability factor of  $\alpha$  of 3.8 is observed.<sup>11</sup> Other polymers prepared by Wulff et. al. can distinguish between dialdehydes, their best case affording an  $\alpha$  of 5.37.<sup>12</sup>

Both Takagishi and Mosbach have synthesized polymers selective for dyes such as methyl orange, rhodanile blue and safranin O.<sup>13,14</sup> Modified silicas are also being developed which are selective for specific dialdehydes,<sup>12</sup> one enantiomer of mannopyranoside derivatives,<sup>15</sup> and dyes.<sup>16</sup>

Reactions conducted on the surface of imprinted polymers have also demonstrated that the polymer has a memory effect. Polymers prepared from (-)-trans-1,2-cyclobutane dicarboxylic diester, after removing the template,

binding fumaric acid to the sites, allowing the system to react with (dimethylamino)methyl-phenyl-oxosulfonium tetrafluoroborate, and finally removing the product from the polymer, yield cyclopropanedicarboxylic acid in 34% yield and 0.05% ee.<sup>17</sup> The utility of these polymers is better illustrated by the regioselective synthesis of truxinic and truxillic acids. The relative amounts of  $\alpha$ , truxillic,  $\beta$ , or  $\delta$  truxinic acid formed from the photochemical dimerization of transphenylcinnamate ester on imprinted polymers are as follows: 100%  $\alpha$  on an  $\alpha$  imprinted polymer, 47%  $\alpha$  and 53%  $\beta$  on a  $\beta$  imprinted polymer and 47.3%  $\alpha$  and 52.7%  $\delta$  on a  $\delta$  imprinted polymer. Since only  $\alpha$  truxinic acid is formed using unimprinted polymers, this study shows the polymers have cavities with high degrees of selectivity.<sup>18</sup>

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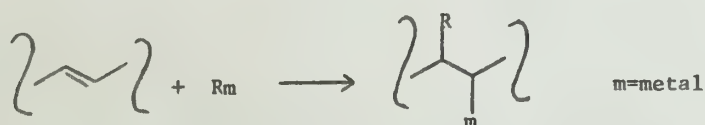
PROXIMITY ASSISTED ADDITION OF ORGANOLITHIUM REAGENTS TO  
CARBON-CARBON MULTIPLE BONDS

Reported by Gordon W. Selling

February 13, 1986

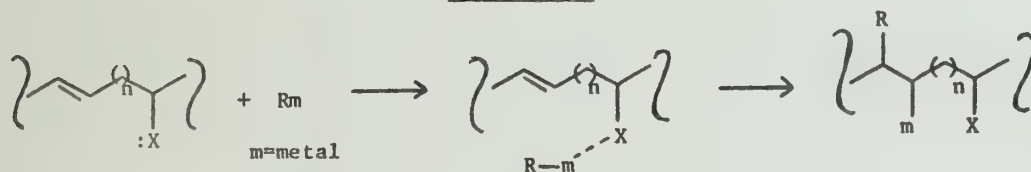
The addition of organometallic reagents to isolated double bonds is an interesting and useful method of creating new carbon-carbon bonds. A major advantage of this methodology is that addition affords an organometallic reagent that may be useful in its own right (Scheme I). Unfortunately, only a

Scheme I



limited number of substrates undergo this reaction. Usually, these substrates are limited to simple alkenes, strained alkenes, intramolecular additions or those reactions which produce a particularly stable anion.<sup>1</sup> The scope of these addition reactions is greatly expanded when a functional group capable of coordinating the organometallic reagent is present. This proximity effect can facilitate addition (Scheme II). Aided by this proximity effect, a variety of

Scheme II



substrates were found to add organometallic reagents.<sup>2</sup> Grignard reagents were among the first found to undergo this addition, although the reaction seems largely restricted to allyl, vinyl and benzyl Grignard reagents.<sup>2</sup> However, a great variety of organolithium reagents will undergo this addition where, as shown in Scheme II, X may be hydroxyl,<sup>3-11</sup> alkoxyl,<sup>12-18</sup> amino,<sup>19-21</sup> amido,<sup>22</sup> or thioalkyl.<sup>21</sup> The addition can be both regio-<sup>3-22</sup> and stereoselective.<sup>6,9,10,13-16</sup>

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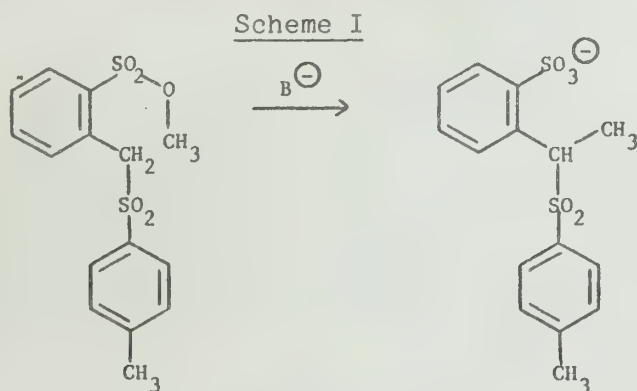


# STUDIES OF NUCLEOPHILIC SUBSTITUTION AT NITROGEN AND OXYGEN

Reported by De-Kai Loo

February 17, 1986

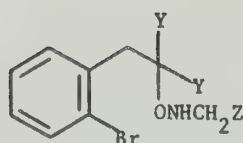
Eschenmoser and coworkers have provided a general approach for studying transition state geometry of the  $S_N2$  mechanisms.<sup>1</sup> They found that in the process of base promoted methyl transfer, shown in Scheme I, the negatively



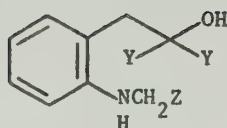
charged carbon attacks the methyl group intermolecularly rather than intramolecularly. The explanation of this result is that the ca.  $180^\circ$  bond angle requirement for the  $S_N2$  process at carbon cannot be achieved in the six-membered ring of the intramolecular reaction.

In formal nucleophilic substitutions at nitrogen or oxygen, the atoms at which the displacement occurs are astereogenic, so transition state geometry cannot be evaluated by analysis of reactant and product stereogeneity.<sup>2</sup> However, the Eschenmoser approach appears applicable. This general approach has been used to investigate nucleophilic substitution at carbon,<sup>3</sup> to investigate radical substitution at sulfur,<sup>4</sup> and to provide a mechanistic distinction for a formal displacement at anionic nitrogen.<sup>5</sup> We now report studies of nucleophilic substitution at nitrogen and oxygen by use of this approach.

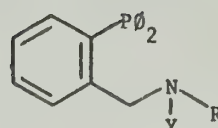
N-Methyl-O-(2-bromophenethyl)hydroxylamine (1) and a mixture of 1- $d_2$  and 1- $d_3$  were synthesized from 2-bromophenylacetic acid in four steps in 20% overall yield.<sup>6</sup> These were used to study the formal nucleophilic substitution at nitrogen of alkoxyamines by organolithium reagents to give a mixture of 2, 2- $d_1$ , 2- $d_2$ , and 2- $d_3$  products. The results of the crossover experiment show that the displacement is intermolecular. Presumably the reaction proceeds by bond angles characteristics of an  $S_N2$  mechanism, bond angles which cannot be achieved intramolecularly.



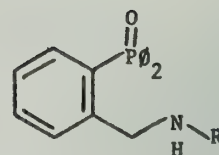
- 1, Y=Z=H  
1-d<sub>2</sub>, Y=D, Z=H  
1-d<sub>3</sub>, Y=Z=H



- 2, Y=Z=H  
2-d<sub>1</sub>, Y=H, Z=D  
2-d<sub>2</sub>, Y=D, Z=H  
2-d<sub>3</sub>, Y=Z=D



- 3, <sup>18</sup>O, Y=OH, R=CH<sub>3</sub>  
3-<sup>18</sup>OH, Y=OH, R=iPr



- 4, R=CH<sub>3</sub>

Nucleophilic substitution at oxygen was studied with N-benzyl(O-di-phenylphosphinyl)-N-methylhydroxylamine (3) and 3-<sup>18</sup>O, both of which were synthesized from 2-bromobenzaldehyde in four steps in overall 21% yield.<sup>7</sup> The kinetic study of oxygen transfer from nitrogen to phosphorous of 3 to 4 and a crossover experiment of 3 and 3-<sup>18</sup>OH were carried out. The results show that formal nucleophilic substitution at oxygen by phosphorous can proceed intramolecularly via a six-membered ring transition state. Apparently, the reaction does not proceed by a classic S<sub>N</sub>2 process. Possible mechanisms of the formal nucleophilic displacement at nitrogen and oxygen will be discussed.

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# ACETYL HYPOFLUORITE, A NEW ELECTROPHILIC FLUORINATING AGENT

Reported by Jian Jian Zhang

February 20, 1986

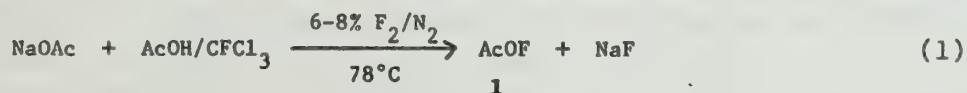
## Introduction

Electrophilic fluorination is an important process in organic chemistry, biology, and pharmacology. The search for electrophilic fluorinating agents has so far produced several reagents. For example, Xenon difluoride,  $\text{XeF}_2$ , and fluoroxy trifluoromethane,  $\text{CF}_3\text{OF}$ , have often been used but only with partial success.<sup>1</sup> In a few cases,  $\text{CF}_3\text{OF}$  adds across double bonds or produces gem-difluorides and ketones.<sup>2</sup> Direct fluorinations with elemental fluorine were also tried and found to be inefficient on a preparative scale.<sup>3</sup> Other fluoroxy reagents, such as  $\text{CF}_3\text{COOF}$  and  $\text{CF}_3\text{CF}_2\text{OF}$ , have also been studied.<sup>4</sup> It was found for several aromatic compounds which were treated with these fluoroxy reagents that low yields of the desired fluorinated compounds were usually obtained along with polymeric tars. These fluoroxy reagents frequently suffer from overreactivity.

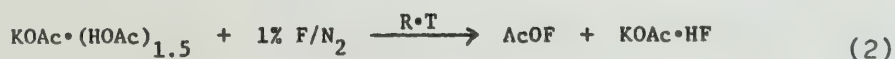
Acetyl hypofluorite,  $\text{AcOF}$  (1), a new electrophilic fluorinating agent, was first synthesized by Rozen and co-workers about four years ago.<sup>5</sup> Acetyl hypofluorite possesses an electrophilic fluorine but is less polarized. Hence, it is milder than the other known fluoroxy reagents. During the short period since its discovery, acetyl hypofluorite has become established as a useful tool for fluorination of activated aromatic rings,<sup>6</sup> carbonyl compounds,<sup>7</sup> and double bonds.<sup>8</sup> Its convenient preparation from  $\text{F}_2$  and its very short reaction times with various organic substrates make it an important reagent for efficient introduction of the radioisotope,  $^{18}\text{F}$ , (half-life=110 min) into the biologically interesting compounds<sup>9</sup> used for the rapidly developing Positron Emitting Transaxial Tomography - PETT.<sup>10</sup>

## Preparation of Acetyl Hypofluorite

Acetyl hypofluorite has been produced by passing a fluorine-nitrogen mixture through a suspension of sodium acetate in a mixture of acetic acid and  $\text{CFCl}_3$  at  $-78^\circ\text{C}$  (Eq. 1).<sup>5</sup> It has also been prepared by the passing of



nitrogen-diluted fluorine either through solutions of ammonium or alkali acetates in glacial acetic acid at room temperature<sup>9a,d</sup> or through the solid  $\text{KOAc} \cdot (\text{KOAc})_{1.5}$  (Eq. 2).<sup>11</sup> In almost all cases, 1 can be prepared and used





in situ without isolation and purification. The identity of **1** was deduced from the nature of the reaction products.<sup>6,7,8</sup> However, **1** has been recently isolated and characterized<sup>12</sup> by passing oxygen or nitrogen diluted fluorine through solid KOAc·2HOAc and trapping the product at -78°C. The crude product was purified by distillation in a high vacuum system. Acetyl hypofluorite is a pale yellow solid at low temperature. It melts at -96°C to a pale yellow liquid. Its boiling point is ca 53°C, at -78°C in 1:1 (v/v) CCl<sub>4</sub>:COCl<sub>2</sub>, its <sup>19</sup>F NMR chemical shift is 168.3 ppm relative to CFCl<sub>3</sub>. This chemical shift is characteristic for fluoroxy groups.<sup>13</sup> The infrared spectrum of **1** was measured in a solid argon matrix and shows bands at 900 cm<sup>-1</sup> (m) and 840<sup>-1</sup> (s) where the O-F bond is expected to absorb.<sup>13</sup> The mass spectrum of **1** shows a molecular peak at 78 and a fragmentation pattern reasonable for the assigned structure.

All spectroscopy properties are consistent with the assigned structure. Decomposition of **1** in a Kel-F container gives nearly quantitatively a 1:1 mixture of CH<sub>3</sub>F and CO<sub>2</sub>. This result is in full agreement with the parallel behavior of CF<sub>3</sub>COOF which similarly decomposes into CF<sub>4</sub> and CO<sub>2</sub>.<sup>14</sup>

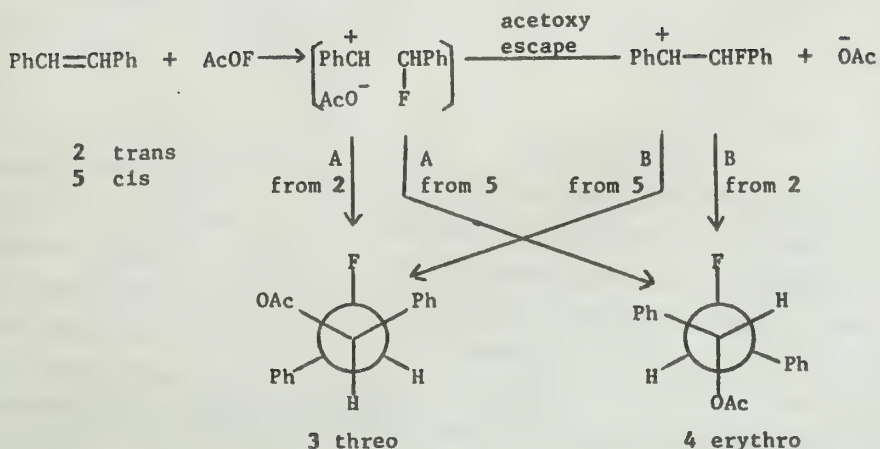
#### Reaction with Unsaturated Systems.<sup>8</sup>

AcOF (**1**) can react with a variety of olefins, including arylethenes, isolated aliphatic double bonds, and rigid olefins, to produce addition products with absolute Markovnikov regiospecificity and high syn addition stereoselectivity.

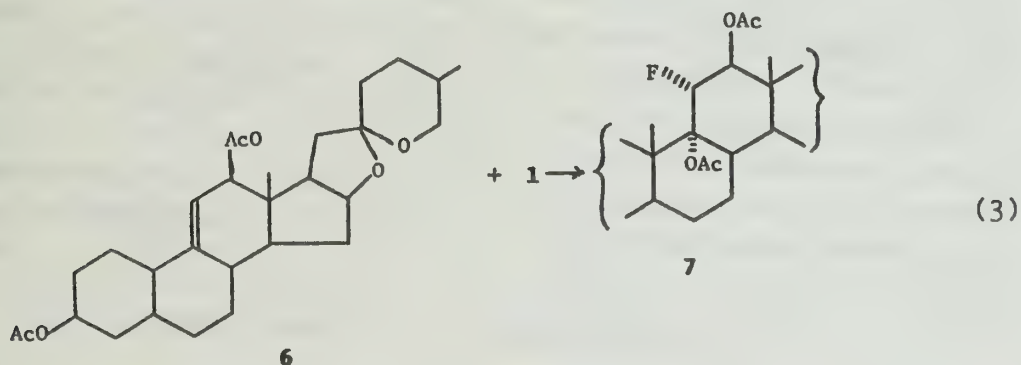
Acetyl hypofluorite reacts with trans-stilbene (**2**) to produce the syn addition product, threo-1-acetoxy-2-fluoro-1,2-diphenylethane, (**3**) in 50% yield and anti addition to attend the corresponding erythro isomer, **4**, in 7% yield. Similar results are obtained when **1** reacts with cis-stilbene (**5**) to give syn addition product **4** in 51% yield and anti addition product **3** in 11% yield. Syn addition occurs from the addition proceeding through a tight ion pair as shown in Scheme 1, pathway A. Anti addition is a result of diffusion of the acetoxy ion from the tight ion pair (pathway B). When **1** reacts with unsymmetrical olefins, such as trans-4-methoxystilbene, the absolute regiospecificity observed is that fluorine is attached to the benzylic carbon next to the unsubstituted ring. This shows the character of electrophilic addition where the positive charge developed in the transition state can be stabilized much more readily by the methoxy substituted ring than by the unsubstituted ring. In this case, however, less stereoselectivity was observed in that the syn addition product (threo isomer) was formed in 42% yield and the anti addition product (erythro isomer) was formed in 15% yield. This result can be explained by the suggestion that the greater stability of the corresponding α-fluorocarbonium ion enhances the ability of the acetoxy ion to escape from the tight ion pair, thus leading to anti addition via



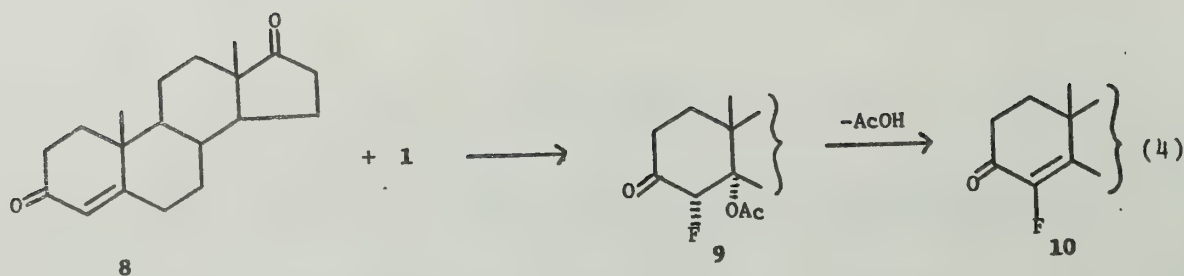
Scheme I



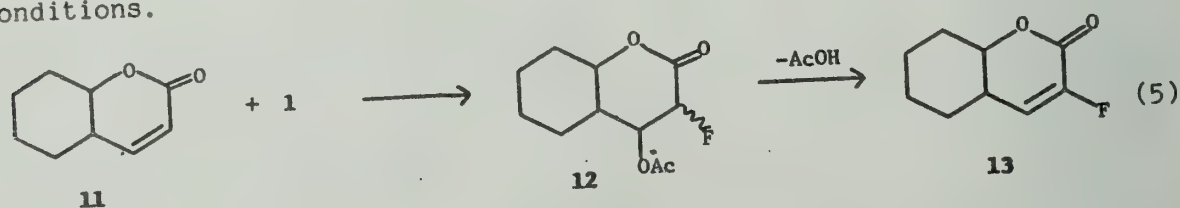
pathway B. It should be pointed out that fluorination also occurs ortho to the methoxy group (vide infra). Treatment of 1 with cyclohexene and 1-dodecene, examples of compounds containing isolated double bonds, gives respectively, only cis-addition product cis-1-acetoxy-2-fluoro-cyclohexane in 60% yield and Markovnikov adduct 1-fluoro-2-acetoxydodecane in 30% yield. Reaction of 1 with rigid olefin 6 affords only product 7 in 90% yield (Eq. 3). This result reflects the fact that 1 can approach the double bond's  $\pi$  electrons only from the  $\alpha$  side of the steroid skeleton.



Acetyl hypofluorite can also be added to deactivated  $\alpha,\beta$ -unsaturated carbonyls, such as aryl substituted  $\alpha,\beta$ -unsaturated carbonyls and rigid cyclic conjugated enones. Treatment of 1 with trans-ethyl cinnamate and cis-ethyl cinnamate gives single product in each case, as the threo and erythro isomers of ethyl 2-fluoro-3-acetoxy-3-phenyl propionate are afforded in 57% and 50% yield respectively. Once again, only cis-addition and Markovnikov products are observed. In the case of rigid  $\alpha,\beta$ -unsaturated ketones, addition of 1 followed by elimination of AcOH gives the  $\alpha$ -fluoro substituted  $\alpha,\beta$ -unsaturated ketone. As in the case of 8 (Eq. 4), spectral evidence is consistent with

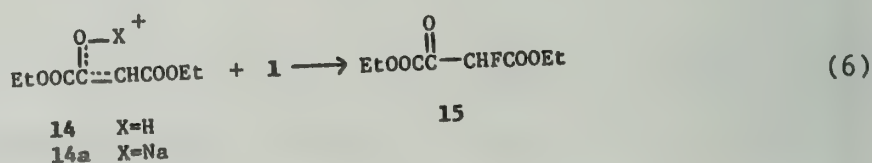


the crude product having the structure of the cis-addition product, 9. However, during purification, AcOH is eliminated to give 10 in 64% yield. Another interesting example is the reaction of 1 with  $\alpha,\beta$ -unsaturated lactone 11 to give cis and trans addition product 12, from which AcOH was eliminated during purification to give final product 13 in almost quantitative yield (Eq. 5). However, treatment of flexible, aryl-free,  $\alpha,\beta$ -unsaturated carbonyls and acetylenes afforded none of the expected products even under forcing conditions.

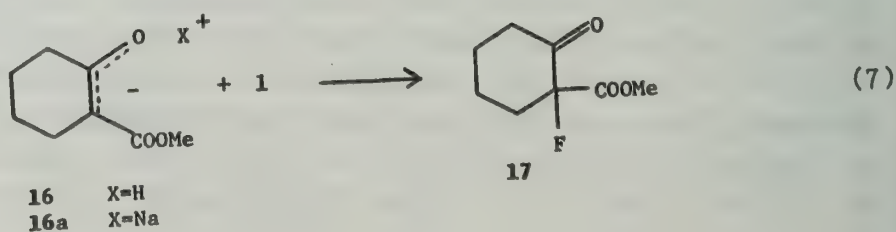


### Reactions with 1,3-Dicarbonyl Derivatives.<sup>7a</sup>

When 1 reacts with 1,3-dicarbonyl compounds, the main products are the 1,3-dioxo-2-fluoro derivatives. Yields depend upon the extent to which the enol form of the 1,3-dicarbonyl derivative is present. Poorly enolizable 1,3-dicarbonyl derivatives give low yields of products, whereas the corresponding sodium enolates give 2-monofluoro derivatives in high yields. For example, reaction of diethyl oxaloacetate (14) with 1 produces diethyl fluoroxaloacetate (15) in 65% yield, however, use of sodium enolate 14a increases the yield to 75% (Eq. 6). Cyclic 1,3-dicarbonyls behave similarly.



As in the case of 16 and 16a, 2-carbomethoxy-2-fluorocyclohexanone (17) was obtained in 30% and 60% yield respectively (Eq. 7). Because



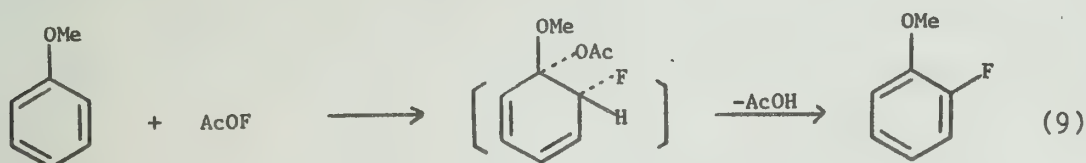
2-carbethoxycyclopentanone has a low enol content, sodium enolate **18** was used instead and, upon reaction with **1**, gives 2-carbethoxy-2-fluorocyclopentanone (**19**) in greater than 90% yield (Eq. 8). It was also reported that **1** reacts



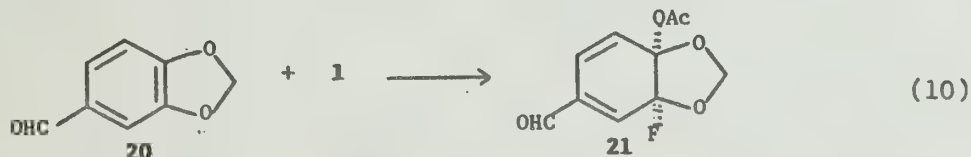
with the metal enolates of monocarbonyl compounds, such as ketones and esters to give the corresponding  $\alpha$ -fluoro-carbonyl compounds.

### Reactions with Activated Aromatic Rings<sup>6</sup>

Acetyl hypofluorite is useful for introducing fluorine in specific sites of aromatic rings. It reacts with activated aromatic compounds at low temperature ( $\sim -75^\circ\text{C}$ ) within seconds to minutes to afford high yields of fluorinated compounds having high ortho/para fluorine ratios. It was believed that the mechanism of electrophilic fluorination is addition - elimination which involves addition of **1** across the higher electron density  $\pi$  region between the ipso and ortho position,<sup>16</sup> followed by elimination of  $\text{AcOH}$  to form the rearomatizing product (Eq. 9). Note the unusually high ortho/para ratio

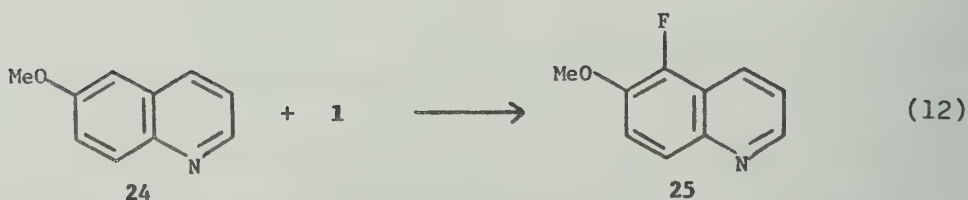
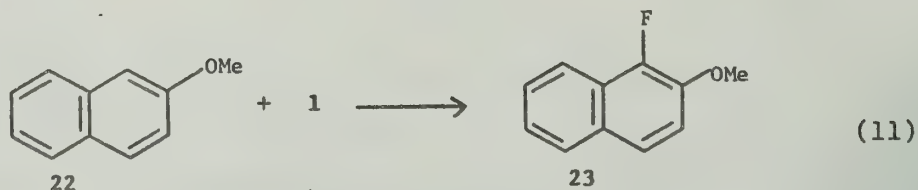


(usually 9:1 ~ 7:1). In some cases even no para isomer was observed. This suggests that the usual  $\pi$ -complex type of substitution is not involved in these reactions. Furthermore, the addition - elimination mechanism is supported by an experiment in which elimination is impossible after addition. Thus, peperonal, **20**, upon reaction with **1**, affords the only cis-addition product **21**, isolated in 55% yield (Eq. 10). Apparently, highly activating group such as

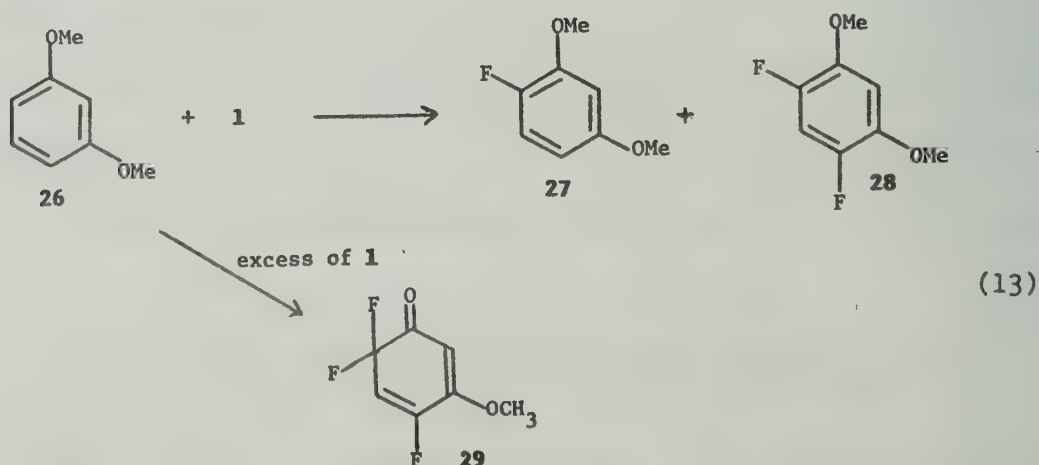


alkoxy or acethylamino are usually necessary. However, phenol, aniline, N-methylaniline, and N,N-dimethylaniline can not survive treatment with **1** which either oxidizes the phenol or attack the nitrogen's lone-pair of electrons. In general, the position of fluorination is in accordance with the electron density of the various sites in the aromatic molecule. Treatment of 2-methoxynaphthalene (**22**) or 6-methoxyquinoline (**24**) with **1** gives, as only

products, 1-fluoro-2-methoxy-naphthalene (23) in 65% yield and 5-fluoro-6-methoxy-quinoline (25) in 75% yield respectively (Eq. 11, 12). The

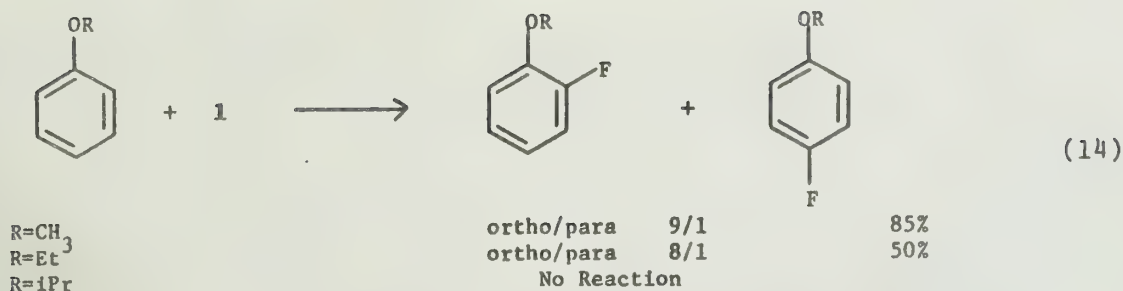


explanation of these results is that the 1,2-bond in 22 is more electron rich than is the 2,3-bond. The 5,6-bond in 24 is more electron rich than the 6,7-bond. It seems that the electrophilic fluorination reaction is more sensitive to steric than to electronic effects. It was found that treatment of 1,3-dimethoxybenzene (26) with 1 gives 27 in 40% yield and 28 in 55% yield. If excess 1 was used, compound 29 was obtained instead of the compound from addition of 1 to 1,2 or 2,3- $\pi$  bonds. This is presumably due to the steric hindrance caused by the two methoxy groups (Eq. 13). Steric effects were



further examined by the reaction of 1 with anisole, ethoxybenzene and isopropylbenzene (Eq. 14). With increasing size of the substituent, the yield decreases dramatically.

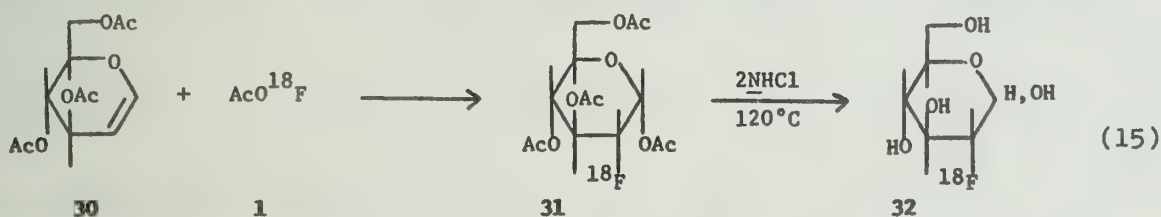




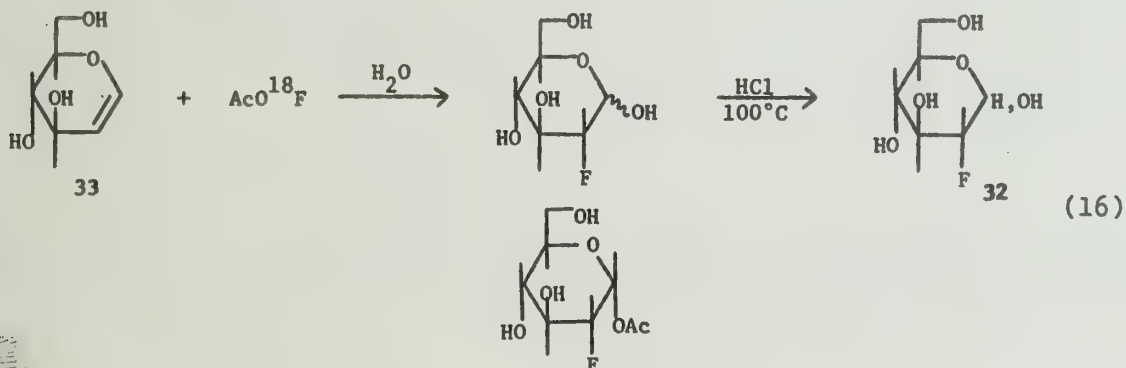
### Synthesis of 2-Deoxy-2-[<sup>18</sup>F]Fluoro-D-Glucose from <sup>18</sup>F-Labeled Acetyl Hypofluorite.

With the development of PETT as a powerful diagnostic tool,<sup>10</sup> organic chemists were motivated to synthesize suitable radiolabeled compounds. The radioisotopes <sup>11</sup>C (half-life 20.4 min) and <sup>18</sup>F (half-life 110 min) are the most suitable for this purpose. Since the discovery of **1** four years ago, it has been widely used to synthesize <sup>18</sup>F labeled D-glucose for PETT.<sup>9a-d,g,i</sup>

Treatment of 3,4,6-tri-O-acetyl-D-glucal (**30**) with **1**, generated in situ from [<sup>18</sup>F]F<sub>2</sub> and ammonium acetate in acetic acid solution at room temperature, gives 2-deoxy-2-[<sup>18</sup>F]fluoro-1,3,4,6-tetra-O-acetyl- α-D-glucopyranose (**31**). After hydrolysis in 2N HCl and purification by column chromatography, 2-deoxy-2-[<sup>18</sup>F]fluoro-D-glucose (2-<sup>18</sup>FDG) (**32**) is afforded in 50% chemical yield and in 20% radiochemical yield (specific activity of 15.5 ~ 20.5 mci/mg)<sup>9a</sup> (Eq. 15). Similarly, 2-<sup>18</sup>FDG was synthesized by passing AcO<sup>13</sup>F



directly to D-glucal (**33**) in aqueous solutions followed by hydrolysis in 37% HCl at 100°C. After purification, 2-<sup>18</sup>FDG was obtained in 34-43% radiochemical yield (> 95% radiochemical purity) with specific activity of 4-6 mci/mg<sup>9g</sup> (Eq. 16). Similar results were obtained by other research groups.<sup>9b,d</sup> In all of



the above cases, it seems as if total stereo- and regioselectivity was attained. However, more careful study<sup>9i</sup> using monosodiumphosphate impregnated silica plates as a separation tool showed that while high regioselectivity was obtained (only a few percent of the addition product having fluorine at C-1 of pyranosylfluoride is formed), only moderate and sometimes even poor stereoselectivity is attained. The percentage of cis-addition product  $^{18}\text{FDG}$  varies from 28-76% and the anti-addition product,  $^{19}\text{FDM}$ , varies from 69-14% depending on the starting materials (TAG vs. Glucel) and solvent (AcOH, NaOAc, NaOH). Other independent research<sup>9i</sup> showed that treatment of TAG with  $\text{AcO}^{18}\text{F}$  does produce 2- $^{18}\text{FDG}$  and 2- $^{18}\text{FDM}$  in 4:1 ratio in polar solvent. However, in a nonpolar solvent such as  $\text{CFCl}_3$ , the reaction produces almost exclusively 2- $^{18}\text{FDG}$  in 95% yield.

### Summary

Acetyl hypofluorite (1) is a more attractive electrophilic fluorinating agent than other known fluoroxy reagents for many organic substrates. Although recently discovered, 1 has become quite a popular reagent in organic chemistry. It is widely used for efficient introduction of  $^{18}\text{F}$  into biologically active compounds for use in the PETT technique.

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## RECENT ADVANCES IN $\beta$ -LACTAM SYNTHESIS

Reported by Lyndon Marble

February 24, 1986

### Introduction

Many naturally occurring  $\beta$ -lactam antibiotics have been isolated, characterized and synthesized over the past half century in the quest to unlock the reasons for their potent antibacterial properties. The penicillins<sup>1</sup> and cephalosporins<sup>2</sup> have been subjected to a wide variety of structural modifications over the past several decades in an effort to find antibiotics with a wider spectrum of activity (particularly against the  $\beta$ -lactamase enzyme) and to provide cheap and efficient syntheses of these biologically important compounds. Several other potent antibiotics have emerged during the search which have given the medicinal community extra weapons against bacterial infection. Some are thienamycins,<sup>3</sup> penems,<sup>4</sup> asprenomycins<sup>5</sup> and most recently, the monobactams.<sup>6</sup> The focus of the majority of the research concerning all these structures prior to 1980 was the manipulation of the functional groups on the lactam ring and in the side chains. Since then much effort has been expended to design efficient syntheses of the  $\beta$ -lactam nucleus itself.<sup>7</sup>

### Historical Perspective

Since the discovery of penicillin, the cephalosporins and other naturally occurring  $\beta$ -lactams, much effort has been expended in attempts to find efficient, versatile syntheses of these compounds. Of the many synthetic routes examined, only a few have shown much promise as being widely applicable.<sup>9</sup>

The most widely explored strategy to prepare  $\beta$ -lactams invokes the closure of acyclic precursors. Treatment of an N-substituted- $\beta$ -amino acid with a carboxylate activator such as acetic anhydride, acetyl chloride, phosphorus trichloride or a carbodiimide gives the desired  $\beta$ -lactam. A related strategy involves the treatment of an imine with a substituted acetic acid derivative in the presence of a tertiary amine to effect ring closure. Cyclization of ketene acetals or enamines by treatment with phenyl isocyanate also leads to lactam formation, but the products are generally unstable.

More recently, the ring expansion of aziridines with thionyl chloride or oxalyl chloride has yielded promising results; however, this method is still in the exploratory stages. Ring contraction of five membered rings has been reported to give  $\beta$ -lactams having a 3-carbonyl substituent. The diastereoselectivity of these methods for cis or trans ring formation, however, is not generally very high. Other related methods of ring formation are plagued by low yields, product instability or lack of generality.

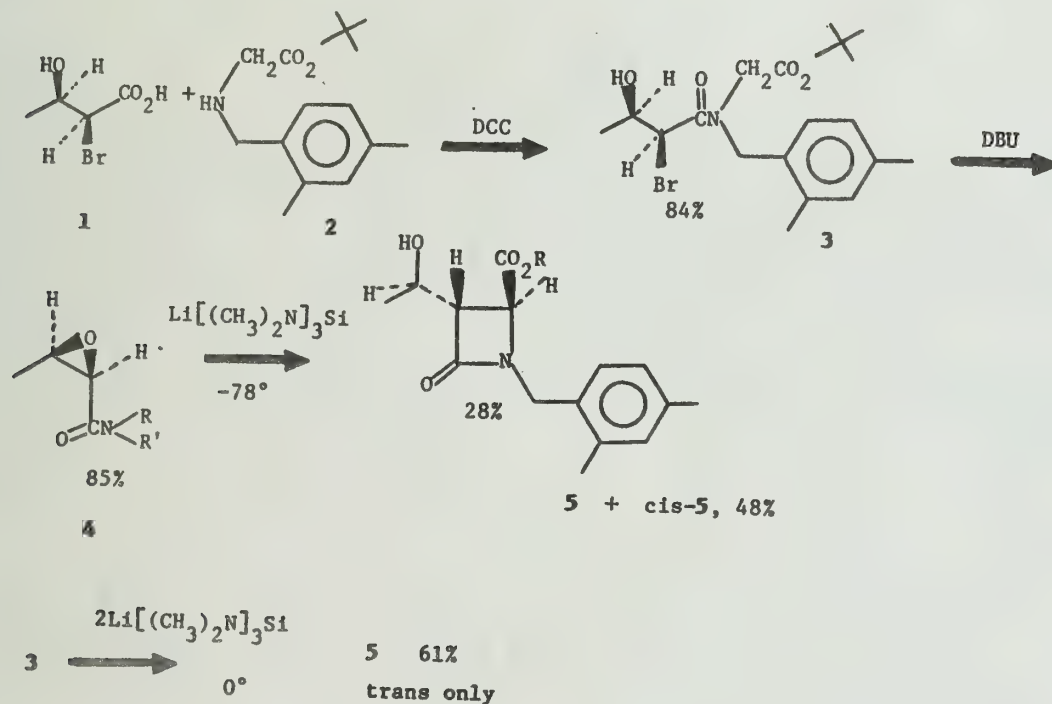


## Stereospecific Syntheses

The most challenging problem facing synthetic chemists is the diastereoselective formation of either the *cis* or *trans*  $\beta$ -lactam. Several workers have used optically active amino acids as the chiral backbone for stereoselective synthesis of  $\beta$ -lactam rings.

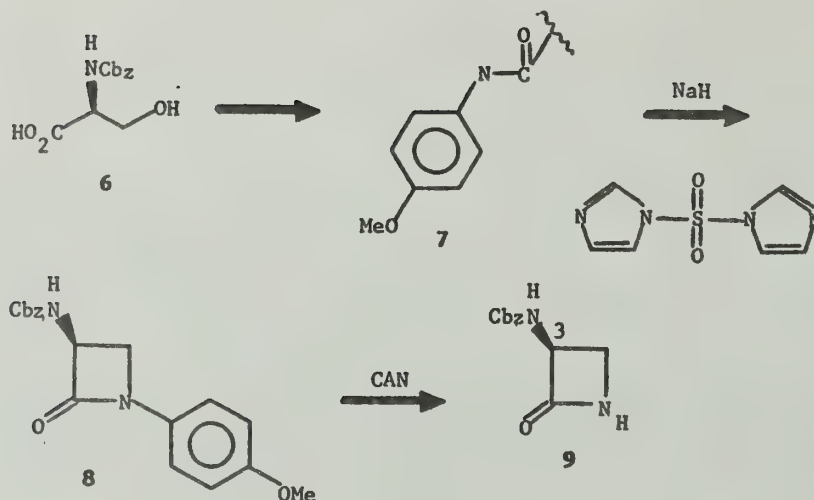
Shiozaki<sup>10</sup> and coworkers began their synthetic approach by condensation of (2*S*,3*R*)-2-bromo-3-hydroxybutyric acid **1** with *t*-butyl N-2,4-dimethoxybenzylglycinate **2** in the presence of N,N-dicyclohexylcarbodiimide to give the amide **3**. Treatment of **3** with diazabicycloundecene (DBU) afforded the epoxide **4**. Cyclization of **4** at  $-78^\circ\text{C}$  with lithium hexamethyldisilazide as base gave a meager 28% of  $\beta$ -lactam **5**. However, cyclization of **3** with two equivalents of the silazide base at  $0^\circ$  gave 61% yield of *trans*-**5** after 1 hour (no *cis* product was detected, Scheme I). Other attempts to cyclize the epoxide directly gave poor yields. Compound **5** was carried on to thienamycin precursors, as were several other analogs of **5**.

Scheme I



Hanessian<sup>11</sup> has reported the use of an imidazole alcohol activating group to effect closure of 3-amido substituted  $\beta$ -lactams. Protection of L-serine as its N-benzyloxycarbonyl derivative **6** followed by amidation with *p*-methoxy aniline afforded **7** in 83% yield (Scheme II). Deprotonation with sodium hydride and activation with sulfonyl(bis-imidazole) at  $-40^\circ$  gave the lactam **8** in 75% yield in optically active form. Removal of the protecting group with ceric

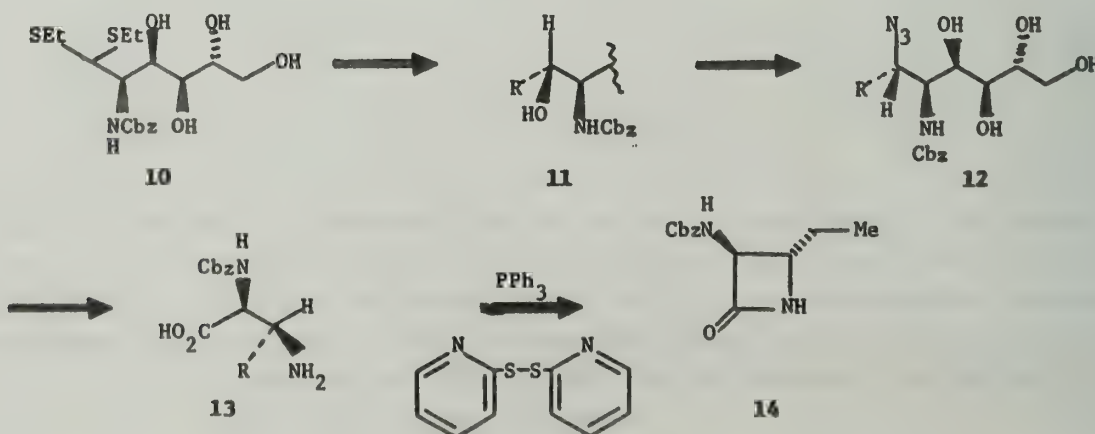
Scheme II



ammonium nitrate provided the known<sup>12</sup> 3-(S)-benzyloxycarbonylamine azetidin-2-one 9 in 44% overall yield from 6. It is important to note that no products from elimination of the imidazolesulfate were detected and that the stereochemical integrity at C-3 had not been destroyed.

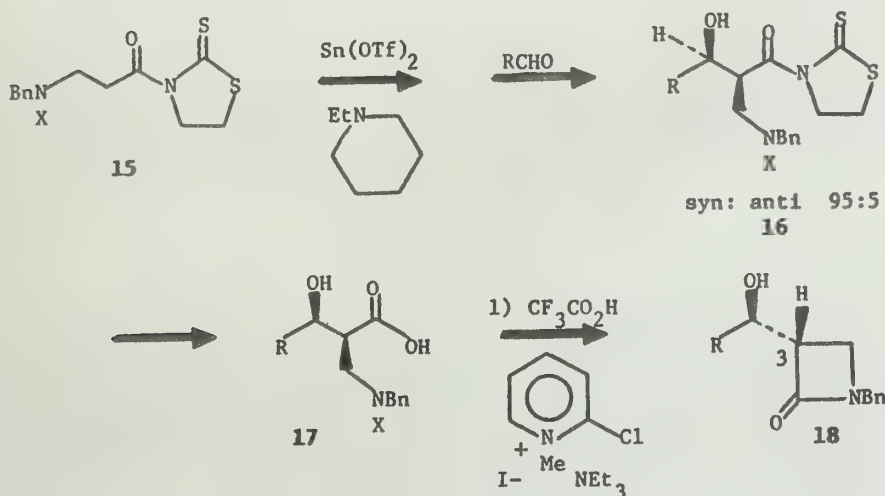
In similar fashion, Hannessian<sup>13</sup> used a second chiral backbone, 2-amino-2-deoxy-D-glucose, to produce an optically active monobactam precursor. The glucose derivative was protected and the amide formed to give 10. Protection, desulfurization and Grignard addition afforded alcohol 11 in 81% for three steps. Mesylation and S<sub>N</sub>2 displacement with azide followed by deprotection gave polyol 12. Oxidative cleavage and reduction afforded amine 13 which was subjected to carboxylate activated cyclization conditions with dipyridyldisulfide and triphenylphosphine to give lactam 14 in 14% yield for 9 steps (Scheme III). A wide variety of other cyclization conditions produced no cyclic products.

Scheme III



Several workers have utilized stereoselective aldol condensations to produce  $\beta$ -lactam precursors. Iwasawa<sup>14</sup> has used a stannous triflate mediated aldol reaction (15→16) to produce intermediate  $\beta$ -hydroxy acid 17, which was subsequently cyclized to afford lactam 18 (Scheme IV). Treatment of the

Scheme VI

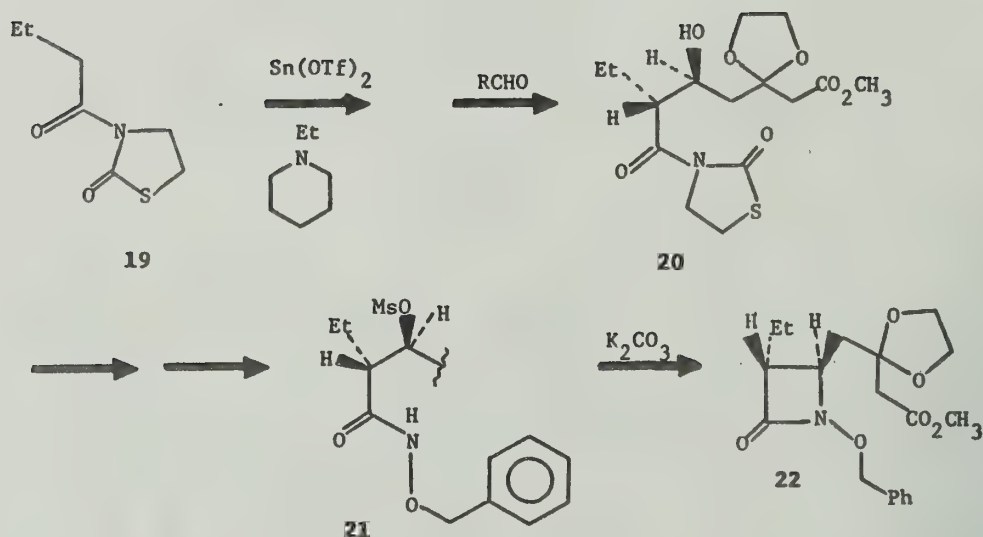


protected  $\beta$ -amino amide 15 with stannous triflate in the presence of N-ethyl-piperidine produced the tin(II) enolate which was allowed to react with a series of aldehydes to give predominantly the syn diastereomer, 16, in each case. The acid was regenerated and cyclized to give  $\beta$ -lactams 18 in 62-80%, with no epimerization of C-3 and containing the hydroxyalkyl side chain important in the thienamycins.

In another stereoselective aldol condensation, Jung and Miller<sup>15</sup> synthesized cis- $\beta$ -lactams starting from 3-butyryl thiazolidine-2-thione 19. Stereoselective aldol condensation gave the  $\beta$ -hydroxy amide 20 in 72% chemical yield and 100% of the erythro isomer. Transamidation (poor yield) followed by mesylation gave hydroxamate 21 which was cyclized under basic conditions to give  $\beta$ -lactam 22 in 12.7% overall yield from amide 20 (Scheme V). This methodology gives trans- $\beta$ -lactams, a feature of olivanic acids and thienamycins. Since ample literature precedent<sup>16</sup> exists for deketalization of  $\beta$ -lactams similar to 22, this route provides a reasonable stereoselective route to carbapenems.

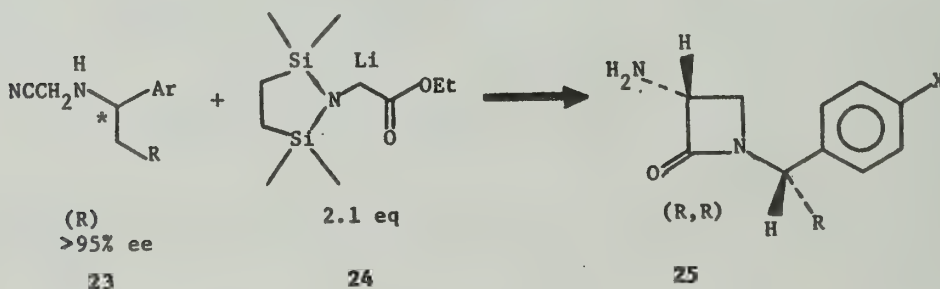
In another stereoselective route, 3-aminoazetidin-2-ones were prepared by Overman and Osawa<sup>17</sup> from an N-substituted glycine ester. Cyanoamine 23 (> 95% ee) was added to 2.1 equivalents of the lithium salt of 24 to afford  $\beta$ -lactam

Scheme V



25 in 11:1 (R,R:R,S) diastereomeric ratio in 72% total yield (Scheme VI). The assignments were made based on chemical shifts of the C-4 hydrogens and were compared to the diastereomers in the 3-amino nocardicinic acid precursors described by Kamio et. al.<sup>18</sup> Several other  $\beta$ -lactams were also produced via this method in both racemic and optically active form.

Scheme VI

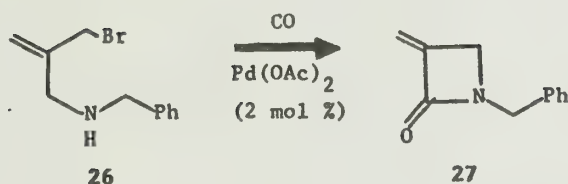


Other Methods

A new method of  $\beta$ -lactam synthesis reported by Ban<sup>19</sup> involves insertion of a carbon monoxide molecule into a Pd(II) complex. The ring closure step is novel in that the carbonyl moiety is not part of the  $\beta$ -lactam backbone prior to cyclization nor is it imbedded in one component of a two component cycloaddition. Allyl vinyl dibromide was reacted with benzyl amine under basic conditions to afford the vinyl bromide 26 which was subjected to cyclization conditions (Scheme VII).  $\beta$ -Lactam 27 was obtained in 67%; typical yields for cyclic products obtained via this route were 60%.

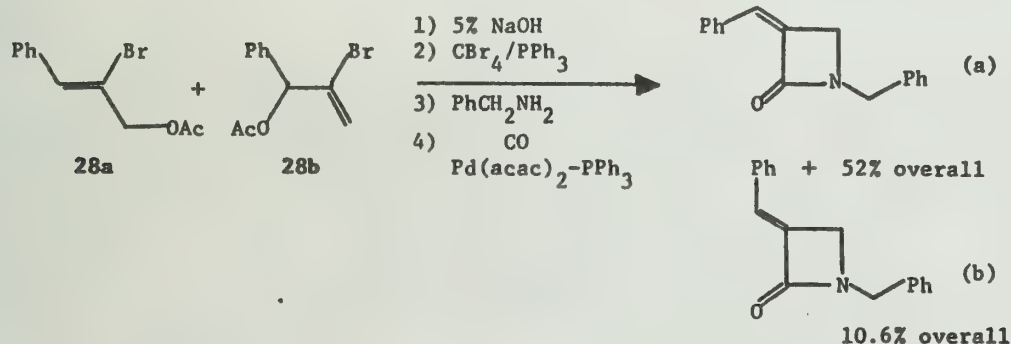


Scheme VII



An alternate route was devised by Ban<sup>19</sup> to synthesize tri-substituted-exo methylene  $\beta$ -lactams. Styrene was transformed into a mixture of allylic acetates, 28a and 28b, by treatment with dibromocarbene and subsequent ring-opening with silver acetate in acetic acid. Both 28a and 28b were taken on to  $\beta$ -lactams by the route shown in Scheme VIII. Several other analogs were prepared by this method in yields of 76 to 90%.

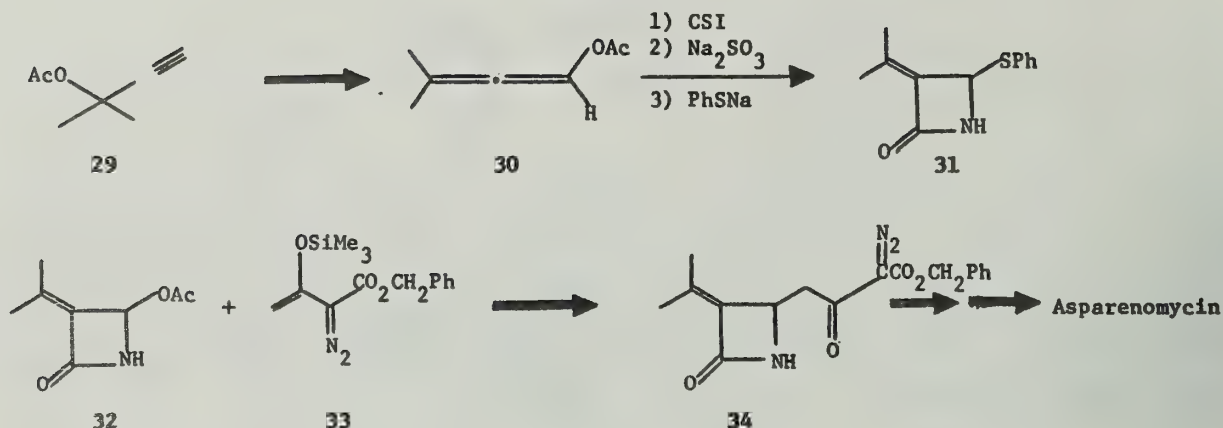
Scheme VIII



Buynak has also synthesized 3-exo-methylene  $\beta$ -lactams by the addition of chlorosulphonyl isocyanate (CSI) to substituted allenes.<sup>20</sup> Propargyl acetate 29 was transformed into allene 30 with silver ion after which the allene was allowed to react with chlorosulphonyl isocyanate. Reductive workup and replacement of the 4-acetoxy substituent with thiophenoxide gave the stable sulfide 31 in 44% overall yield. The intermediate 4-acetoxy  $\beta$ -lactam, 32, reacts with silyl enol ether 33 to produce  $\beta$ -lactam 34. Diazo compound 34 was elaborated to an asparenomycin analog (Scheme IX).

A route complimentary to 4-alkoxy substituted  $\beta$ -lactam formation was reported recently by Claudi.<sup>21</sup> His route is a variation on the classical acid chloride-imine cycloaddition in which imidates are condensed with various acid chlorides. Imidate 35 was allowed to react with acid chloride 36 and three equivalents of triethylamine. After 12 hours,  $\beta$ -lactam 37 was isolated and

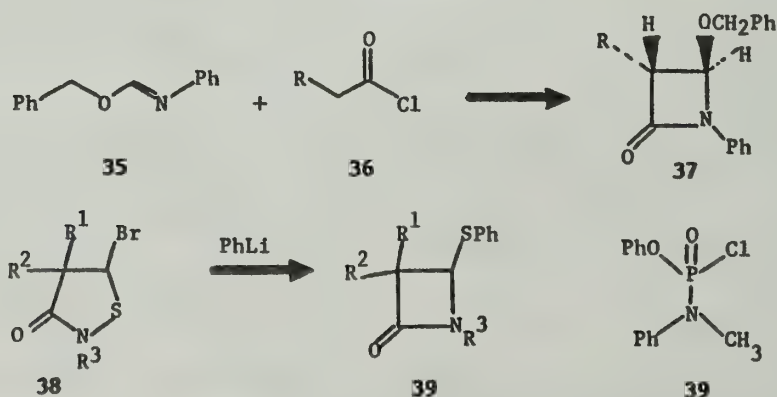
Scheme IX



determined to be the trans isomer ( $J=1$  Hz, H-C3, H-C4; Scheme X). The authors have also begun exploration of the formation of  $\beta$ -lactams from imidates and ketenes.

Easton<sup>22</sup> has used ring contraction of isothiazolidinones to give penicillin precursors. The lactam ring was formed by treatment of 38 with phenyllithium in ether; product lactam 39 was obtained in five steps in 34% overall yield (Scheme X). This method provides entry into  $\beta$ -lactam systems

Scheme X



which are doubly substituted in the 3-position. This feature provides the possibility of elaboration to a variety of penicillin derivatives which would be difficult to obtain by other methods. In addition to the example shown, other  $\beta$ -lactams have been made by this route and a related sequence in which the phenyls at position 3 have been replaced with hydrogen, benzyloxyamido, and methyl. Variation of the substituents at sulfur and nitrogen was also examined.

Several short reports of new routes to  $\beta$ -lactams have appeared recently. The reaction of azabutadienes with ester enolates was described by Ohshiro and coworkers to proceed in high yield via an intermediate aza allylanion.<sup>23</sup> It was also shown that either  $\beta$ -lactams or N,N-bi-lactams could be formed in the reaction of 2,3-diazabutadiens with ester enolates depending on the reaction conditions.

Sandhu and Sain reported the synthesis of 3-amido-3-alkyl trisubstituted  $\beta$ -lactams in the reaction of an oxazolinone with imines.<sup>24</sup> Variations in substituents led to several  $\beta$ -lactams in yields from 60 to 80%.

Saccharin had also been used as an activating group to form  $\beta$ -lactams. Tokutake<sup>25</sup> has reported the condensation of N-acylated saccharins with imines in triethylamine to provide mono- and multicyclic  $\beta$ -lactams in acceptable yield (65 - 82%).

### Summary

Many new routes to  $\beta$ -lactams have appeared recently and indicate the immense effort being spent to produce  $\beta$ -lactams in high chemical yields and with high diastereoselectivity. Some of these methods have been listed here but a wide variety of methods has not been discussed. Several good collections of reports about  $\beta$ -lactam antibiotics and their syntheses cover an even wider range of functional group manipulations which lead to important antibiotics. The problem of diastereoselectivity has received extensive attention in the past few years and reasonable success has been achieved. Much work is still to be done since a method of general applicability is not yet available.

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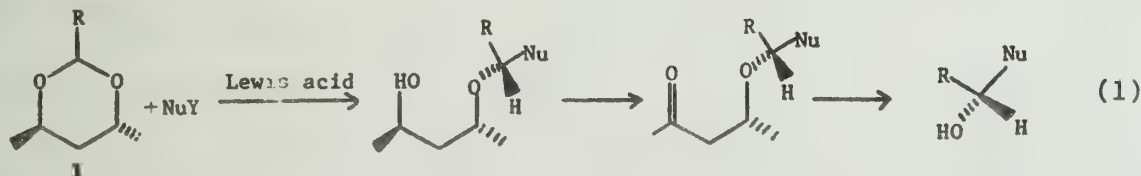
# ASYMMETRIC SYNTHESIS VIA CHIRAL ACETAL TEMPLATES

Reported by Wei Jane Liao

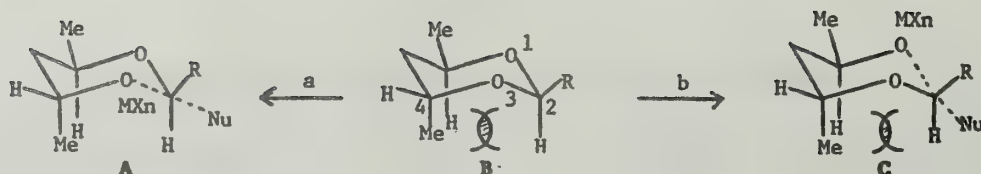
February 27, 1986

The Lewis acid catalyzed reactions between acetals and nucleophiles such as allylsilanes<sup>1</sup> and Grignard reagents<sup>2</sup> are well-known. Recently, Johnson and, to a lesser extent, Kishi<sup>3</sup> explored the Lewis acid promoted coupling of chiral acetals with various nucleophiles. The reactions proceed stereoselectively and after removal of the chiral auxiliary, lead to secondary hydroxylic compounds.

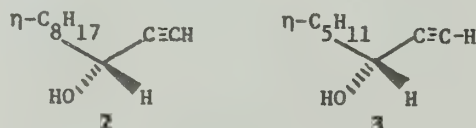
Acetals derived from (R,R)-2,3-butanediol as well as (R,R)- and (S,S)-2,4-pentanediols have been used in their studies. In the cyclization of chiral acetals or polyolefinic aldehydes,<sup>4,5</sup> Johnson found that acetals from either of the chiral 2,4-pentanediols possess a number of advantages over their five-membered-ring counterparts: (a) both the R,R and S,S forms of the diols are readily available from the asymmetric hydrogenation of acetylacetone;<sup>6</sup> (b) the diastereoselectivity of the cyclization is improved; (c) the chiral auxiliary is easily removed in high yield without racemization of the new chiral center by  $\beta$ -elimination of the derived ketone (eq. 1). Thus, nucleophiles such as allyltrimethylsilanes,<sup>5</sup> silylacetylenic compounds,<sup>7</sup> cyanotrimethylsilanes,<sup>8,9</sup> organometallic reagents,<sup>10</sup>  $\alpha$ -silyl ketones and enol silyl ethers<sup>11</sup> have been employed in the coupling reaction in which a predominance of either diastereomeric form can be obtained by using either (R,R)- or (S,S)-2,4-pentanediols. In general, the selectivity of the coupling process depends on (a) the nature of the substituent R in the acetal 1; (b) the structure of the nucleophile; (c) the type of catalyst; (d) the reaction conditions (e.g. solvent, temperature, concentration and the addition order of the reagents). Titanium tetrachloride is the most common Lewis acid employed in these reactions. Better selectivity has been obtained by using a more hindered catalyst:  $6\text{TiCl}_4 \cdot 5\text{Ti}(\text{O}i\text{Pr})_4$ .<sup>12</sup>



The transition state of the coupling process is suggested to be the  $S_N2$ -like transition state A where the relatively large 2,4-diaxial H/Me interaction in the ground state B is relieved by a lengthening of the 2,3 bond (path a).<sup>9</sup> No such interaction is relieved in the transition state C (path b) which affords an antipode form in the new chiral center; therefore, path a is favored.



Optically pure secondary alcohols obtained from asymmetric syntheses have been shown to be important synthetic intermediates. For example, alcohol 2 is an intermediate in the synthesis of methyl (E)-2,4,5-tetradecatrienoate, a pheromone of the male dried bean beetle.<sup>13</sup> Alcohol 3 and its enantiomer have been used as intermediates in the synthesis of the  $\omega$ -side chain of prostaglandins (15R)- and (15S)-PCB<sub>1</sub>.<sup>14</sup> Undoubtedly, more information concerning the scope and limitations of the Lewis acid catalyzed acetal coupling reaction will be obtained in the future.



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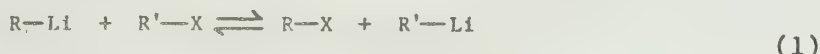
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# THE MECHANISM OF HALOGEN-LITHIUM EXCHANGE

Reported by Timothy J. Musick

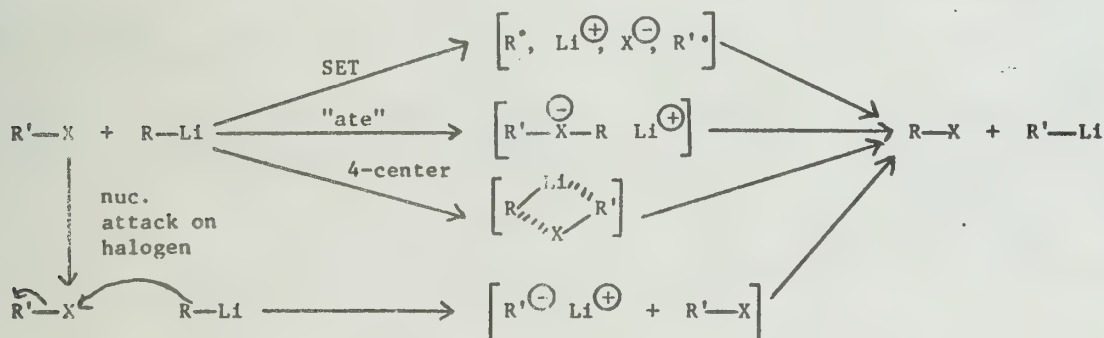
March 3, 1986

In the 1930's it was discovered that some simple organolithium compounds could be reacted with organic halides to prepare other lithiated species via a halogen-metal exchange reaction (Equation 1). These reactions have become



quite useful for the preparation of unstable or functionalized lithium reagents, as they generally occur rapidly and in good yield, while coupling between the electrophilic and nucleophilic organic species is rarely a competing process. This brings into question the mechanism of such a reaction. It had long been considered to involve a four-center transition state,<sup>1-4</sup> but in recent years evidence has been accumulated for some other possible mechanisms, including single electron transfer (SET),<sup>5-12</sup> nucleophilic attack on halogen,<sup>13-15</sup> and through an "ate" complex<sup>16-17</sup> as an intermediate (Scheme I). The SET pathway was first suggested by Russell in 1964. Since that report, evidence for this mechanism has included electron spin resonance (esr),<sup>5,12</sup> chemically induced dynamic nuclear polarization (CIDNP),<sup>6-9</sup> radical rearrangement studies,<sup>10,11</sup> and radical scavenging studies.<sup>4,18</sup>

Scheme I



The "ate" complex is a rather recent hypothesis and as yet is supported only by kinetic studies.<sup>16</sup> The mechanism involving nucleophilic attack on halogen is consistent with the presence of radical intermediates. In this report we will examine some recent findings on the mechanism of halogen-lithium exchange.

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# SYNTHETIC, BIOSYNTHETIC AND BIOLOGICAL STUDIES OF BICYCLOMYCIN

Reported by Kaiming Li

March 6, 1986

Bicyclomycin is an antibiotic isolated by two Japanese groups in 1972.<sup>1,2</sup> Since then, numerous biological, biosynthetic and synthetic studies have been carried out. This report is a brief review of these studies.

**Isolation.** Bicyclomycin was isolated from culture filtrates of Streptomyces sapporonensis and Streptomyces aizunensis.<sup>1,2</sup>

**Structural Identification.** The structure of bicyclomycin was elucidated by nuclear magnetic resonance spectroscopy and by x-ray diffraction analysis.<sup>3,4,5</sup> Bicyclomycin has an exomethylene group primary, secondary and two tertiary hydroxy groups and four asymmetric centers (Fig. 1).

**Biological studies.** Studies of biological activity have shown that bicyclomycin is active against gram-negative bacteria and inactive against gram-positive bacteria.<sup>6-9</sup> The mechanism of action of bicyclomycin was found to be distinct from that of other known classes of antibiotics. Preliminary studies by Iseki et. al. indicate that the primary action of bicyclomycin may be due to interference with the biosynthesis of lipoprotein.<sup>8</sup>

**Biosynthesis.** The biosynthesis of bicyclomycin by Streptomyces sapporonensis was studied and it was found that production of bicyclomycin is enhanced most effectively in the presence of equimolar amount of L-leucine and L-isoleucine. Nicotinamide and  $Fe^{++}$  are essential cofactors in the biosynthesis.<sup>10</sup> Commercial production of bicyclomycin from fermentation broths has been achieved by the Fujisawa Co.<sup>11</sup>

**Total Synthesis.** Many attempts have been made to synthesize bicyclomycin<sup>12-16</sup> and three total syntheses of bicyclomycin have been reported recently.<sup>17-19</sup> There are two key steps in the total syntheses. One is the regiospecific cyclization<sup>13,17</sup> of the side-chain on the diketopiperazine ring (I) to give the bicyclo[4,2,2] ring (II). The other is the aldol condensation<sup>17-19</sup> of an aldehyde and the carbanion generated at the bridge-head position of the bicyclo[4,2,2] ring (II) (Figure 2).

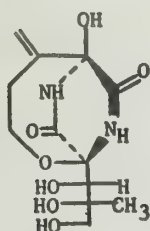


Figure 1.  
bicyclomycin

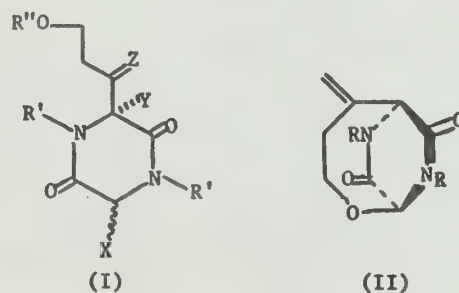


Figure 2.

Bibliography

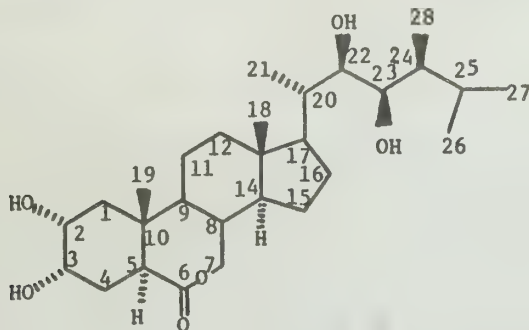
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# SYNTHETIC AND STRUCTURE-ACTIVITY STUDIES OF BRASSINOSTEROIDS

Reported by Wei Dai

March 10, 1986

Brassinosteroids, including Brassinolide<sup>1</sup> and its analogues,<sup>2</sup> comprise a new class of plant growth-promoting compounds. Brassinolide (1) isolated from rape pollen, is a potent plant growth-promoter. The structure and stereochemistry of (1) (2 $\alpha$ ,3 $\alpha$ , 22R,23R-tetrahydroxy-24S-methyl-B-homo-7-oxa-5 $\alpha$  cholestan-6-one) were determined by spectroscopic data, including x-ray crystallography in 1979.<sup>1</sup> Subsequently, Thompson<sup>3</sup> and Takatsuto et al.<sup>4</sup> have independently focused attention on the structure-activity relationships and synthetic methodologies of brassinolide and its analogues.



Brassinolide and its analogues, with either a modified steroidal nucleus or a modified side chain have been mainly investigated in the bean second-internode assay and the rice lamina inclination test. The results indicate the following structural requirements<sup>5-6</sup> for significant plant growth-promoting activity: 1) 2 $\alpha$ ,3 $\alpha$ -diol in the A-ring, 2) 7-oxalactone B-ring, 3) alkyl groups at C-24, and 4) cis-configuration of C-22,C-23 vicinal diol.

In general, the synthetic strategy for AB-ring construction follows that reported by Thompson<sup>7</sup> in 1979 and Siddall<sup>8</sup> in 1980. The 2 $\alpha$ ,3 $\alpha$ -diol is introduced by dihydroxylation of double bond at C-2; Baeyer-Villiger oxidation<sup>9</sup> of the 6-one derivatives provides the 7-oxalactone steroidal nucleus of brassinosteroid.

Asymmetric introduction of the 22,23-diol is the key step in construction of the side chain. Direct oxidation of the  $\Delta^{22,23}$  double bond gives either a mixture of cis-diols,<sup>4b,10</sup> or the unnatural 22S,23S-diol.<sup>11</sup> The 22R,23R-diol of the side chain has been selectively introduced by one of three methods: 1) Sharpless Asymmetric epoxidation;<sup>12</sup> 2) a chelation-controlled Grignard reaction<sup>13</sup>; and 3) a chelation-controlled addition of a metallated butenolide.<sup>14</sup>

Because of the natural scarcity and the remarkable biological activity of the brassinosteroids, this study continues to attract attention.

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# THE SHARPLESS ASYMMETRIC EPOXIDATION: MECHANISM AND SYNTHETIC UTILITY

Reported by Brad Henke

March 13, 1986

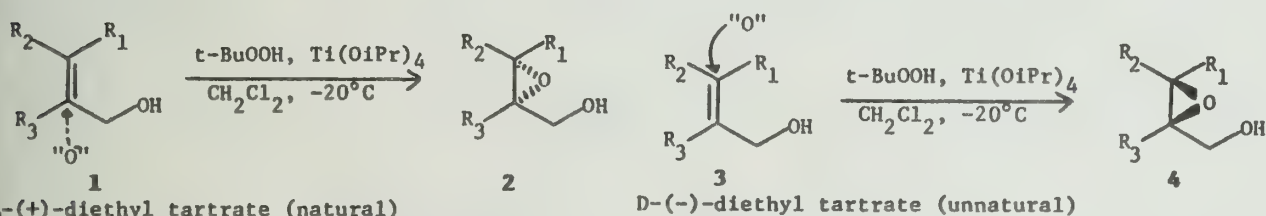
## Introduction

The ability to prepare asymmetric compounds enantioselectively is an important and rapidly expanding area of organic chemistry.<sup>1</sup> Epoxidation is especially valuable in asymmetric synthesis because epoxides can be opened in a stereospecific manner to produce two contiguous chiral centers. Olefin epoxidation with metal-hydroperoxides<sup>2</sup> and peroxyacids<sup>3</sup> has been exploited in many syntheses, and the mechanism of this procedure has been reviewed several times.<sup>4</sup> This seminar will cover one of the most powerful of these epoxidation methods, the Sharpless enantioselective epoxidation of allylic alcohols.<sup>5</sup>

## Background

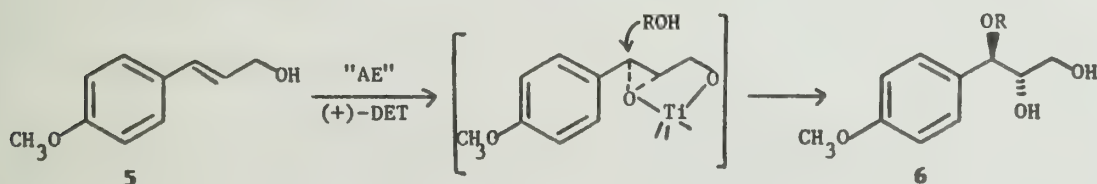
Perhaps the most useful aspect of the Sharpless asymmetric epoxidation (referred to hereafter as AE) is the accuracy with which one can predict the stereochemical outcome of the reaction. Regardless of the substitution pattern on the olefin, use of (+)-tartrates leads to epoxidation from the underside, while use of (-)-tartrates leads to epoxidation from the top when the allylic alcohol is drawn as in Scheme I. The yields on most allylic alcohols range

Scheme I



from 70-90% with ee's greater than 85%. However, very reactive allylic alcohols are prone to titanium-mediated ring opening reactions (Scheme II), and some (Z)-allylic alcohols react sluggishly and give poor ee's.

Scheme II



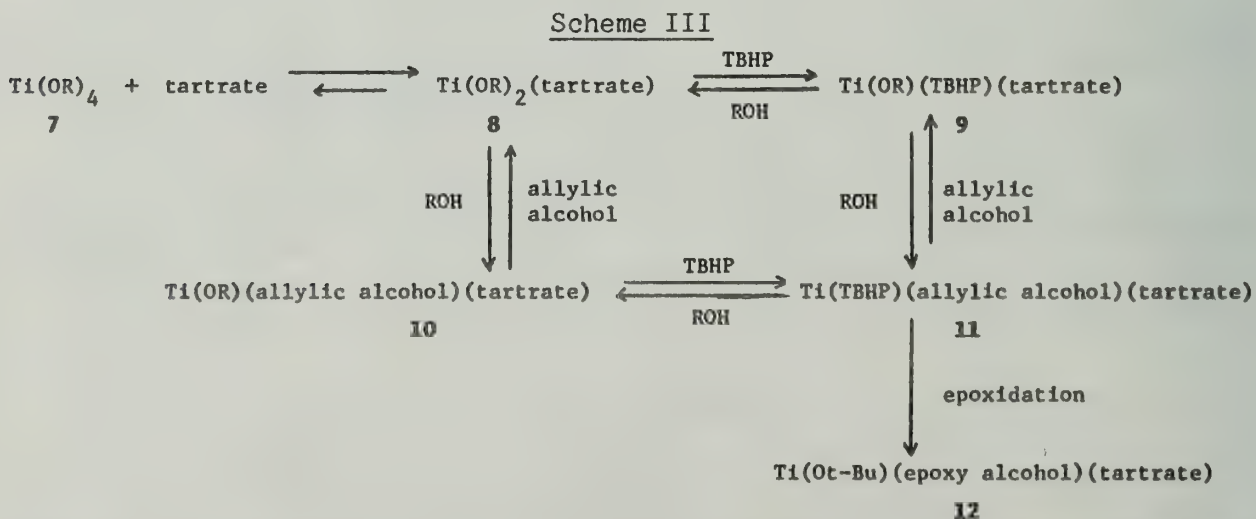
The AE involves the addition of an allylic alcohol and tert-butyl hydroperoxide (TBHP) to a titanium alkoxide-tartrate catalyst. It is similar in nature to other transition-metal catalyzed epoxidations,<sup>2</sup> except that it employs dialkyl tartrates or tartramides to induce asymmetry.

The use of transition metal alkoxides other than titanium results in much poorer asymmetric induction.<sup>6</sup> The unique ability of titanium is explained in terms of its reluctance to form oxo ligands,<sup>7</sup> thus enabling it to coordinate simultaneously with the hydroperoxide, allylic alcohol, and the divalent tartrate.

Sharpless and coworkers have surveyed a large number of chiral ligands,<sup>8</sup> and found that the dialkyl tartrates and tartramides are by far the most stereoselective. In addition, both enantiomers of tartaric acid are inexpensive, readily available and the diesters and diamides are easily obtained in enantiomerically pure form.<sup>9</sup> The optimal ratio of titanium to tartrate is 1:1.2; use of a 1:1 or 1:<1 ratio results in less than optimum enantioselectivity.<sup>10</sup> The reaction is in principle catalytic, but often stoichiometric amounts of the titanium-tartrate complex are needed.

### Mechanism

The origin of asymmetric induction of the AE has only just recently been postulated.<sup>8</sup> The combination of equimolar amounts of a titanium tetraalkoxide, 7, with a tartrate diester releases 2 equivalents of alcohol and forms complex 8, of stoichiometry  $[Ti(OR)_2(tartrate)]_x$  (Scheme III). Addition of TBHP and allylic alcohol displaces the two remaining alkoxide ligands forming the



"loaded complex", 11.<sup>8</sup> Oxygen transfer then occurs to afford the coordinated epoxide and t-butoxide, 12; these are then replaced by more allylic alcohol and TBHP to complete the catalytic cycle. Kinetic studies done by Sharpless have proven the first-order dependence on catalyst and TBHP<sup>11</sup>.

Although the actual structure of the "loaded complex" 11 has not been determined due to the lability of the ligands and the fluxional properties of the system, Sharpless has obtained X-ray structural data for several titanium-tartrate derivatives.<sup>12</sup> This data (Figure 1) shows a dimeric complex

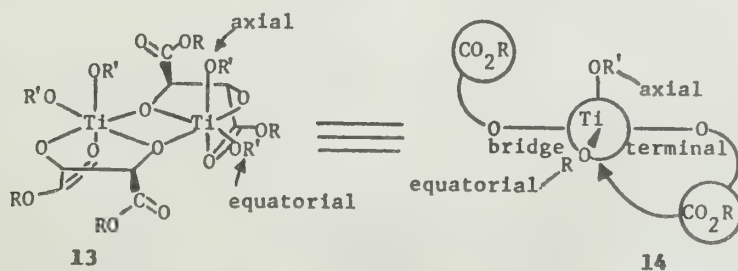
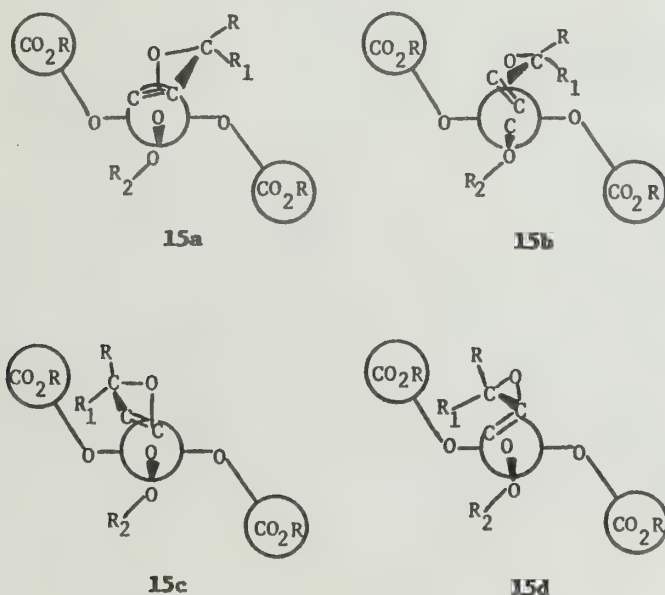


Figure 1

with titanium adopting a six-coordinate pseudo-octahedral geometry. In this orientation the ester groups block two of the diagonal quadrants of space around the metal. Sharpless then makes three assumptions that lead to the proposal of a highly-ordered transition state. First, the peroxo oxygen distal to the peroxide alkyl group is transferred to the olefin.<sup>4c,13</sup> Second, the proximal peroxo oxygen interacts strongly with the titanium.<sup>14</sup> Finally, the favored approach of the olefin is along the axis of the O-O bond being broken.<sup>15</sup> Molecular models indicate that the alkyl hydroperoxide should displace the equatorial alkoxide with the O-O axis oriented perpendicular to the plane, with the allylic alcohol thus occupying the axial position. In this arrangement there are four allylic alkoxide conformations which allow attack on the peroxide in an  $S_N2$  fashion (Scheme IV). Steric interactions disfavor

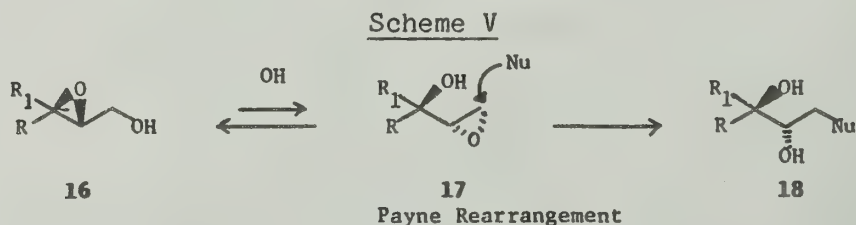
Scheme IV



structures **15c** and **15d**. The observed enantioselection in the AE is consistent with **15a** being preferred over **15b**. Sharpless offers several suggestions<sup>8</sup> for this preference, which is presumably stereoelectronic in nature.

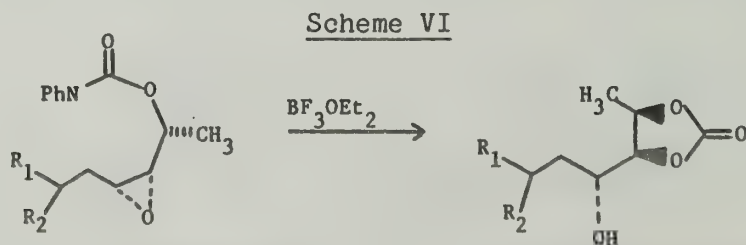
### Transformations of 2,3-Epoxy Alcohols

2,3-Epoxy alcohols can undergo highly regio- and stereoselective nucleophilic opening at either C-2 or C-3, and have latent reactivity at C-1 via the Payne rearrangement<sup>16</sup> (Scheme V).



Sharpless and Masamune<sup>17</sup> have obtained C-1 substitution with satisfactory yields using thiolates, secondary amines, and  $\text{BH}_4^-$  as nucleophiles. The scope of the reaction can be increased if the terminal epoxy alcohol is isolated; this allows addition of nucleophiles such as azides, cuprates, acetylides, cyanide and  $\text{LiAlH}_4$  with high yield and regiocontrol.<sup>18</sup> In addition, the 2,3 epoxide moiety can be left intact by converting the alcohol to the mesylate or tosylate followed by reaction with various nucleophiles.<sup>19,20</sup>

While some simple 2,3 epoxy alcohols can be opened regioselectively at C-3,<sup>21</sup> more often the opening is regiorandom. However, a number of methods for regiocontrolled ring opening have been developed. Roush and coworkers<sup>22</sup> use an internal nucleophile in the form of urethane attached to the hydroxyl moiety (Scheme VI) to obtain attack exclusively at C-2. Interestingly, Sharpless



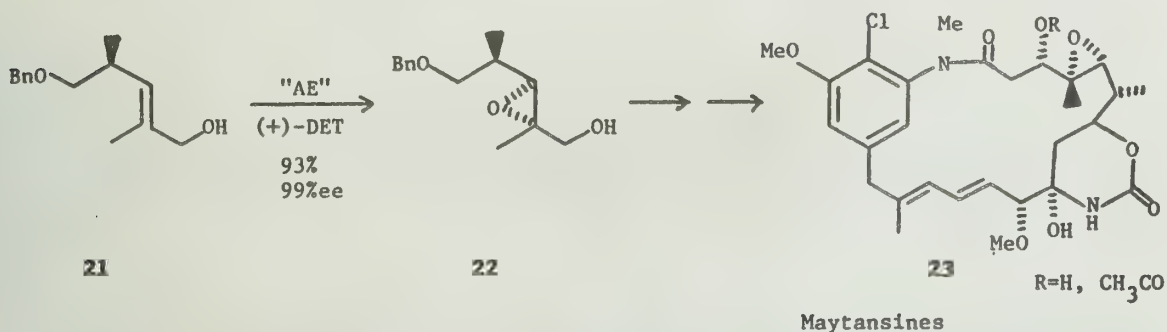
reports a very strong preference for attack at C-2 when nucleophiles are added to 2,3 epoxy alcohols in the presence of titanium tetraisopropoxide.<sup>23</sup> It has also been shown<sup>24</sup> that Red-Al is extremely selective in reducing epoxides at C-2 to afford 1,3-diols. Modest C-2 selectivity has also been observed when 2,3 epoxy acids and amides are attacked by amines and thiolates; however, if titanium tetraisopropoxide is added to the reaction, the regioselectivity completely reverses and attack at C-3 is greatly favored.<sup>25</sup>



## Use of AE in Syntheses

Since its discovery, the AE has been a key step in the synthesis of several natural products containing the epoxide moiety.<sup>19,20</sup> In Meyers' and Hudspeth's synthesis of maytansines, allylic alcohol **21** was epoxidized in excellent yield and enantiomeric excess to yield **22**<sup>26</sup> (Scheme VII).

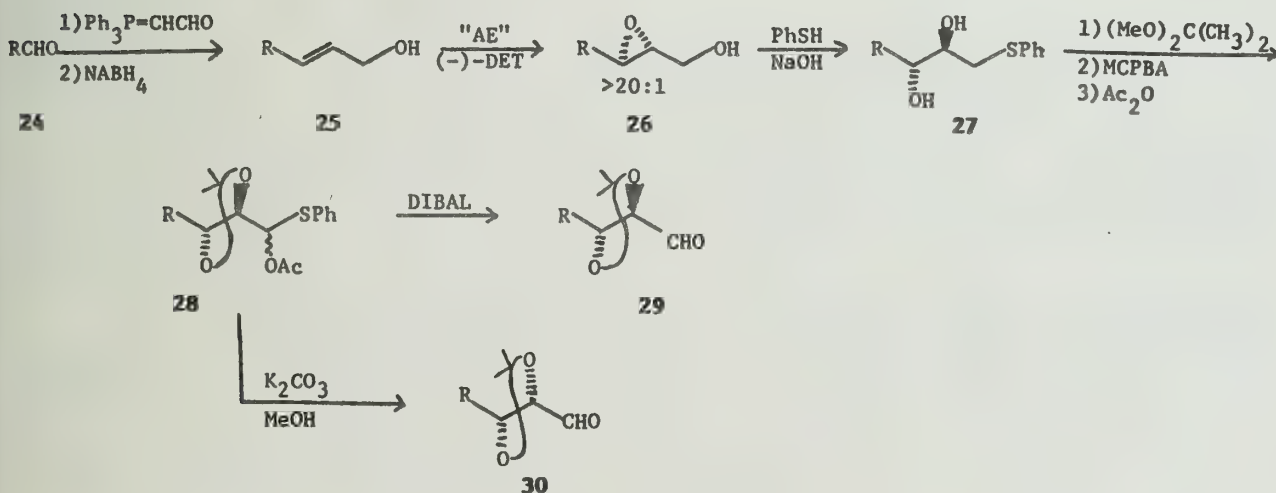
Scheme VII



Even more numerous are the natural products in which the epoxide formed by the AE has been used as an intermediate in the synthesis,<sup>19,27-34</sup> usually being transformed into the necessary functionality by the methods discussed above.

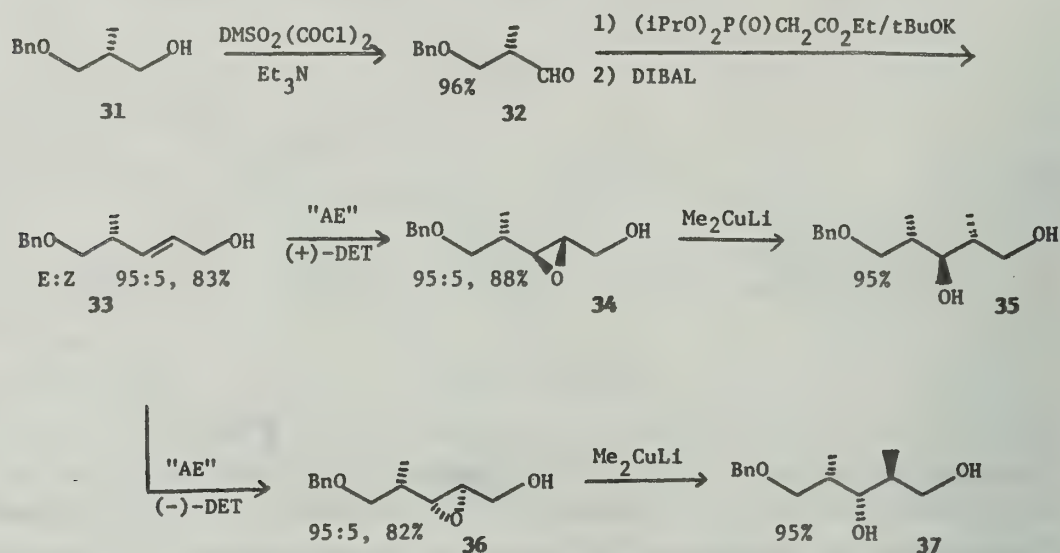
The AE has had its greatest impact in the synthesis of polyhydroxylated compounds such as carbohydrates and macrolides. In this context, the AE has been used in reiterative sets of reactions to construct numerous chiral centers. One such sequence, developed by Masamune and Sharpless,<sup>17a</sup> is a two-carbon chain extension involving four steps; this strategy is exemplified in the synthesis of the two diastereomeric aldehydes in Scheme VIII. A similar approach has also been used by Sharpless in the synthesis of swainsonine.<sup>35</sup>

Scheme VIII



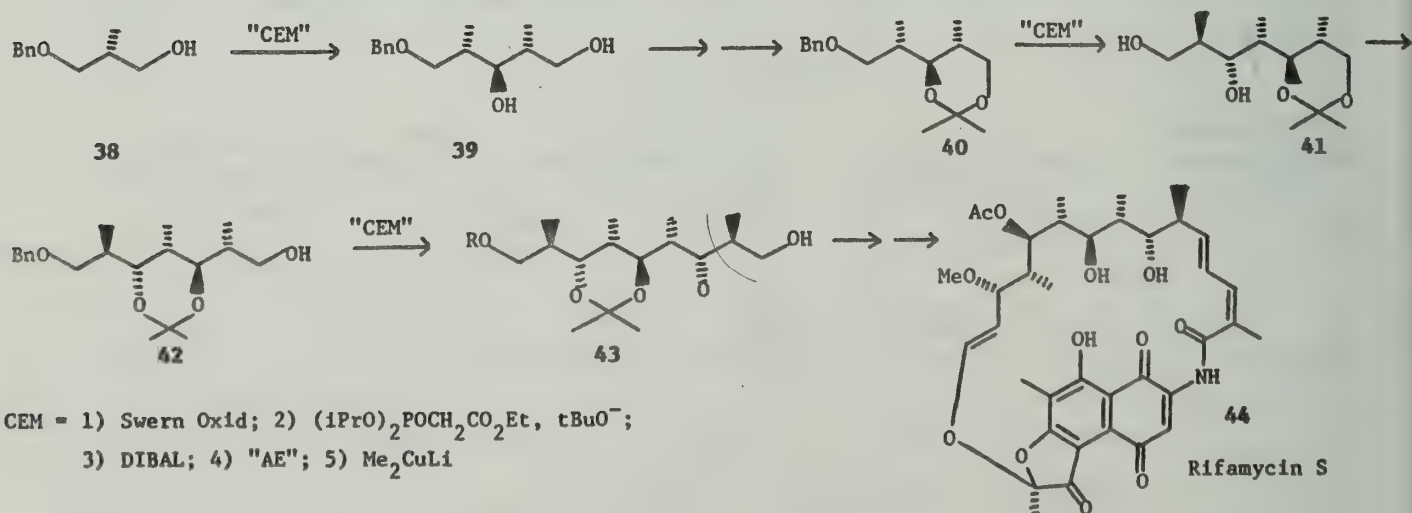
Another reiterative methodology, shown in Scheme IX, has been developed by Kishi<sup>36</sup> to synthesize polyhydroxylated compounds. Kishi has used this "chain

Scheme IX



extension method" (CEM) to synthesize a key intermediate in the total synthesis of rifamycin S<sup>36a</sup> (Scheme X). Finally, the AE was also used extensively by Kishi in the structural determination of palytoxin, one of the most complex toxins isolated.<sup>37</sup>

Scheme X



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## RECENT ADVANCES IN STEREOSELECTIVE MICHAEL ADDITIONS

Reported by Martin B. Wolk

March 17, 1986

The Michael addition has been the subject of much study and many reviews on the scope of the reaction have been published.<sup>1</sup> Recent interest in chiral and diastereoselective syntheses has provoked a number of groups to study stereoselectivity in the Michael addition. Heathcock, Evans, and others have applied new techniques to influence the stereochemical outcome of the aldol reaction.<sup>2</sup> Using related techniques, researchers have shown that both enantio- and diastereoselective Michael additions can be achieved under the correct conditions.<sup>3</sup>

### Enantioselective Michael Additions

Enantioselectivity in the Michael addition has been approached in two distinct ways. Chiral bases, base complexes, and organometallic catalysts interact with achiral Michael donors and acceptors to give an enantiomeric excess of the major adduct via external asymmetric induction. Alternatively, chiral auxiliaries can be used to modify Michael donors or acceptors to yield optically active products via internal asymmetric induction.

Early studies with the cinchona alkaloid derived catalyst (R)-2-(hydroxymethyl)-quinuclidine **1** showed that achiral Michael precursors led to optically active products (Scheme I, Table I).<sup>4</sup> Polymer-immobilized cinchona alkaloids have been prepared by alkylating the quinuclidine nitrogen to a polymeric support and by copolymerization of the vinyl moiety with acrylonitrile (e.g. **2**, from quinine).<sup>5</sup> The former method shows little enantioselectivity as a Michael catalyst, presumably because one of the possible sites of chelation has been eliminated. The latter method, however, yields Michael products exhibiting as much as 42% ee. Recently, more sophisticated studies involved the use of chiral base complexes. Cram and Sogah used chiral crown complexes, such as **3**, as catalysts and isolated products with 20-98% ee.<sup>6</sup> They proposed that the initial chiral host-base complex undergoes an exchange after the generation of an enolate. The chiral host-enolate complex reacts with the Michael acceptor in an enantiospecific fashion governed by the steric restrictions imposed by the host. Koga achieved an enantioselective conjugate addition of dithioacetal derivatives mediated by a chiral (L)-phenylalanine derived ligand.<sup>7</sup> After generation, the lithiated dithiane complexes with the chiral host and interaction is again dictated by the sterically limited approach of the lithiated dithiane-chiral host complex. Prochiral acceptors yield products with up to 67% ee. Chiral cobalt complexes

Scheme I

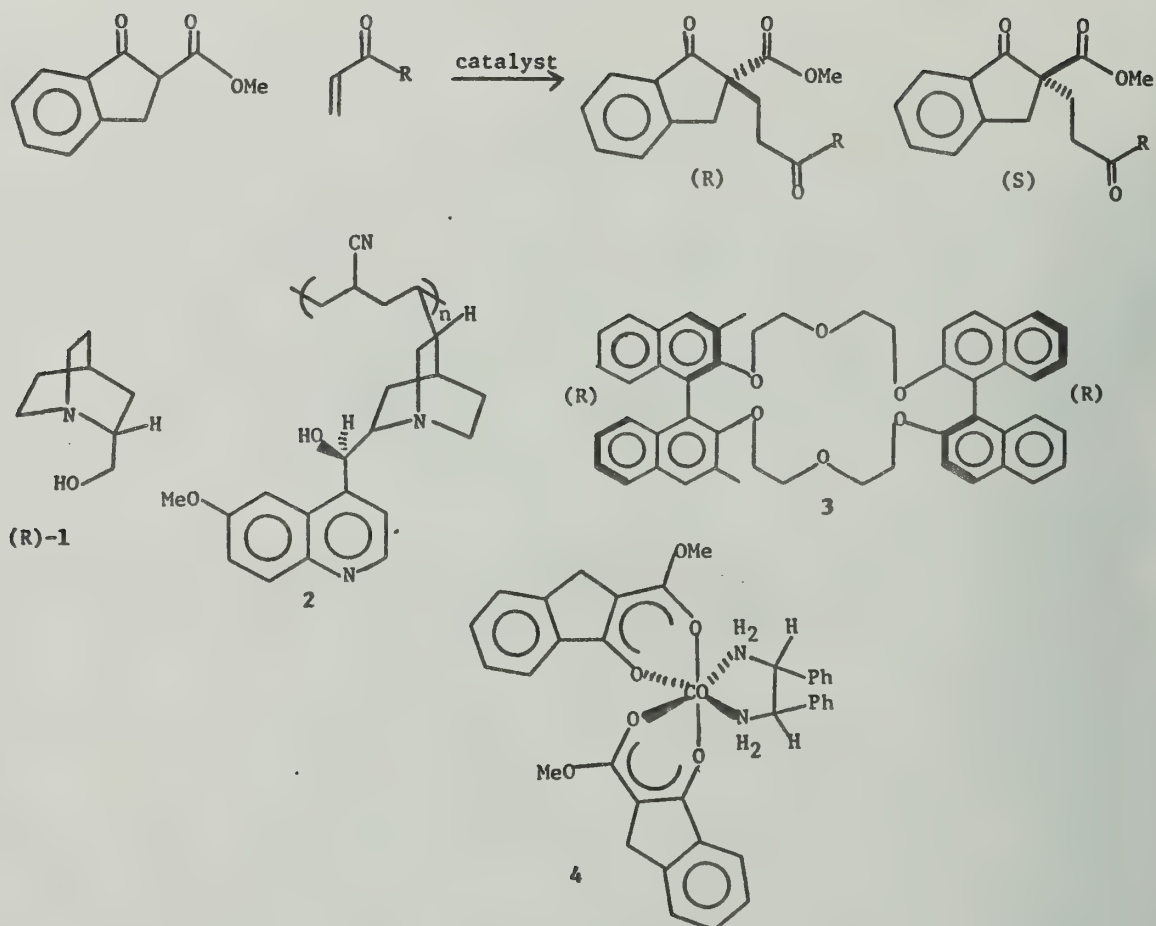


Table I: Enantioselectivity via External Asymmetric Induction:  
Catalytic Addition of Methyl-2-Carboxy-1-Indanone  
to Acrolein and MVK.

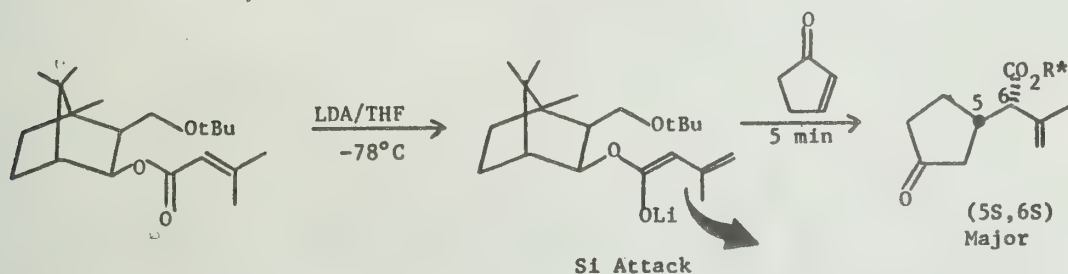
Catalyst	R	% ee	% Yield	Configuration of Major Enantiomer	Reference
1	H	--	--	--	4
2	Me	30	98	S	5
3	Me	~99	48	R	6
4*	Me	66	50	R	8

\*The catalyst is actually the corresponding  $\text{Co}(\text{acac})_2$  diamine complex. The  $\text{Co}(\text{enolate})_2$  diamine complex is shown for clarity.

have been shown to undergo ligand exchange in the presence of  $\beta$ -keto esters to form enolate complexes.<sup>8</sup> The bidentate enolates (e.g. 4) can be oriented in a limited number of ways when they occupy the four available ligand sites. Products are obtained from the use of these catalysts in up to 80% yield and 66% ee. All of these approaches suffer from the fact that the chiral complexes were designed for very specific substrates and therefore the scope of each is limited.

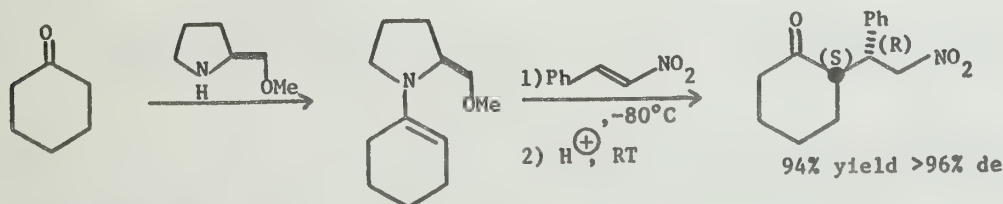
Chiral auxiliaries have been used to modify both Michael acceptors and donors with much success. Oppolzer has applied his work with crotonate esters of chiral camphor-derived alcohols to the Michael addition (Scheme II).<sup>9a,b</sup> Lithium dienolates of these esters add to 2-cyclopentenone via an lk approach

Scheme II



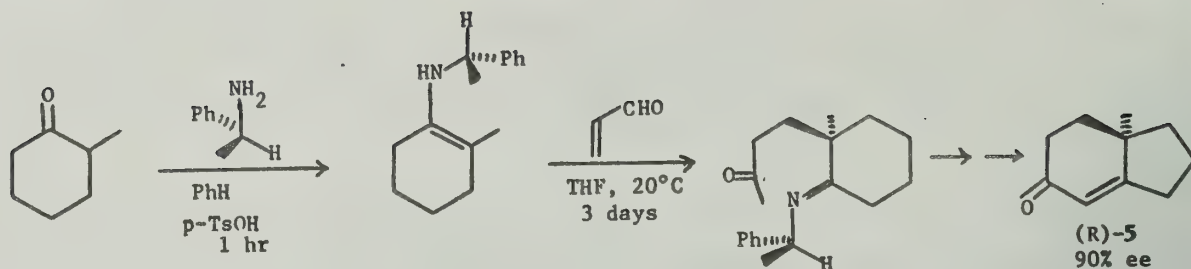
to give l-1,5-ketoesters.<sup>10</sup> Chiral amines and hydrazines are useful as chiral auxiliaries because they provide a simple route to chiral enamines and hydrazones from achiral ketones. Application of these compounds to the Michael addition stems from their initial use by Yamada in the alkylation of cyclohexyl enamines derived from proline esters and cyclohexanone.<sup>11</sup> Seebach used a proline derived enamine as the donor in a reaction with  $\beta$ -nitrostyrenes (Scheme III).<sup>12</sup> The products were  $\alpha$ -alkylated cyclohexanones of >90 % ee which were

Scheme III



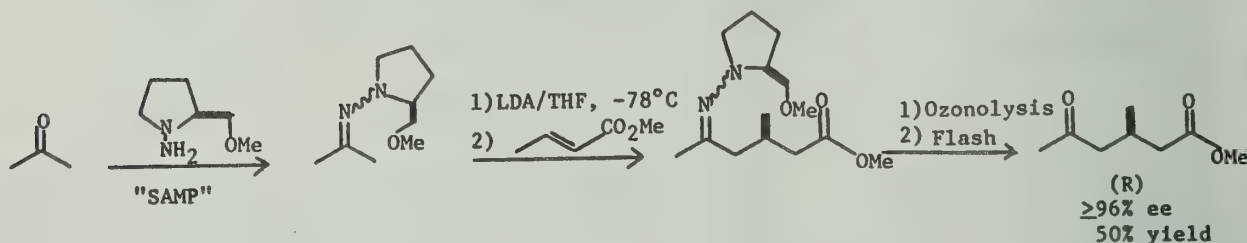
which were generated through a lk,ul-1,4 approach. Imines prepared from readily available (S)-1-phenylethylamine also exhibit enantioselectivity in reactions with electron deficient alkenes such as methyl vinyl ketone or methyl acrylate. Pfau used this process in a highly enantiospecific (>90 % ee) synthesis of (R)-(-)-hydrindenone 5 (Scheme IV).<sup>13</sup> In similar studies, Enders used (S)- or

Scheme IV



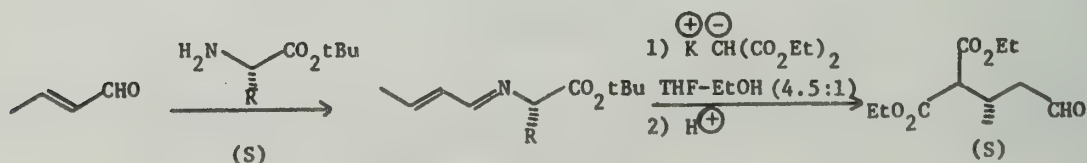
(R)-1-amino-2-methoxy-pyrrolidine (SAMP or RAMP) as a chiral metalloenamine auxiliary.<sup>14</sup> He found that SAMP/RAMP metalloenamines add to a number of  $\alpha,\beta$ -unsaturated esters to give adducts of >90% ee (Scheme V). Chiral amines can also be used to modify Michael acceptors. Koga used chiral  $\alpha,\beta$ -unsaturated

Scheme V



aldimines prepared from crotonaldehyde and t-butyl esters of amino acids as acceptors in reactions with diethyl malonate (Scheme VI).<sup>15</sup> In spite of the numerous possibilities for side reactions, the additions proceed with moderate

Scheme VI



chemical yield and optical yields up to 86%. All of the above methods involve the use of chiral auxiliaries which are either readily available (proline esters, SAMP, RAMP, etc.) or easily obtained from commercially available materials by well documented procedures (i.e. Oppolzer's camphor derived auxiliary). In addition, the placement and removal of the auxiliaries typically involve mild reaction conditions (i.e. enamine formation and hydrolysis). The scope of the reactions of the modified Michael precursors also tends to be broader than that of the external asymmetric induction systems.

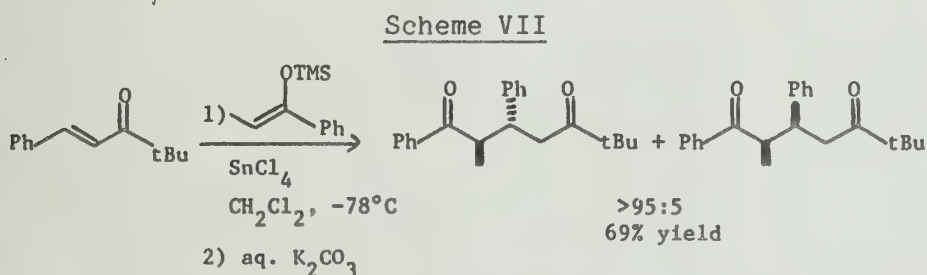


### Diastereoselective Michael Additions

Diastereoselectivity in the Michael reaction has been a difficult problem because of the nature of the base catalyzed addition. Early cases of systems which show slight diastereoselectivity were attributed to an eight-membered closed transition state in which the cation is coordinated to both oxygen atoms and bond formation occurs through the least sterically congested transition state.<sup>16</sup>

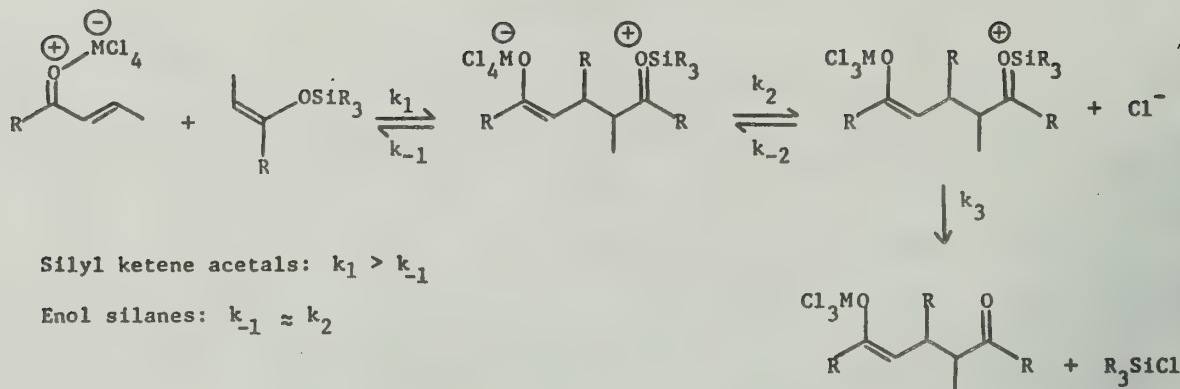
In 1974, Mukaiyama demonstrated that enol silanes react with  $\alpha,\beta$ -unsaturated ketones under Lewis acid catalysis to give 1,5-dicarbonyl compounds in good yields.<sup>17,18</sup> This reaction, dubbed the Mukaiyama-Michael addition, allowed synthesis of Michael products under mild conditions (i.e.  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ) which do not favor the multitude of side reactions usually associated with the base catalyzed reaction. Mukaiyama later extended the scope of the reaction to include silyl ketene acetals as donors.<sup>19</sup> RajanBabu subsequently showed that the Mukaiyama-Michael may also be initiated by tris(dimethylamino) sulfonium difluorotrimethyl siliconate (TASF).<sup>20</sup>

Heathcock exploited the mild reaction conditions to investigate the mechanism and stereochemistry of the new addition. Using both enol silanes and silyl ketene acetals as donors, and a wide variety of enones as acceptors, the Heathcock group performed the reaction with either  $\text{TiCl}_4$  or  $\text{SnCl}_4$  as catalysts (Scheme VII).<sup>21</sup> The silyl ketene acetals showed a tendency for lk approach



while the enol silanes favored ul approach. Product geometry was found to be independent of donor geometry. The rationalization for the discrepancy in reaction products is that silyl ketene acetals add to enones under kinetic control to form the relatively stable delocalized oxonium ion. This addition product ionizes and then irreversibly loses the corresponding silylchloride. The kinetic addition is thought to occur through the least sterically crowded open transition state, the lk approach. Reactions with enol silanes, on the other hand, are thought to be under thermodynamic control since the initial equilibrium is less favorable. Retroaddition competes with ionization and desilylation and the thermodynamic product, that of ul approach, is formed in excess (Scheme VIII).

Scheme VIII

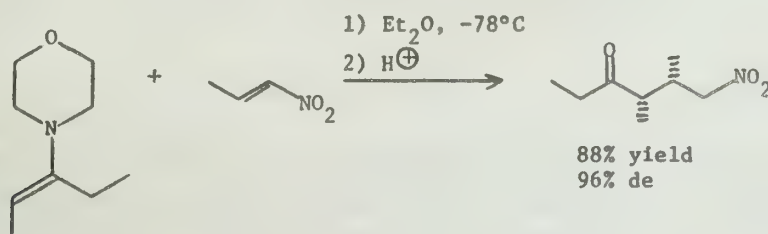


By combining the ideas from his work on Mukaiyama donors and chiral aldehydes with those from the Mukaiyama-Michael addition, Heathcock showed that Mukaiyama donors add to chiral enones with high diastereofacial differentiation.<sup>22</sup> As before, enol silanes showed a preference for ul topicity. In addition, (tert-butyl dimethylsilyl)oxy compounds lead to greater diastereoselectivity than the corresponding (trimethylsilyl)oxy compounds presumably because the increase in steric bulk leads to greater differences in transition state energies. A higher degree of substitution at the nucleophilic carbon of the donors also leads to increased diastereoselectivity. With prochiral donors, one of the four possible diastereometric products predominates. The actual mechanism for the diastereoselective Mukaiyama-Michael addition is still in question. Several inconsistencies with the proposed kinetic-thermodynamic control theory were apparent in Heathcock's latest publication.

Nitroalkenes have been used extensively as Michael acceptors.<sup>23a-c</sup> Several thorough studies on the geometric implications of cyclohexyl enamine attack of nitroalkenes have created the foundation on which recent studies by Seebach and Mukaiyama are based. Seebach found that morpholine enamines add to nitroalkene (Scheme IX).<sup>24</sup> The rate determining step, the addition to form the nitronate, is readily reversible and the product is the result of thermodynamic control. The diastereoselectivity is very high in all of the additions given (>90 % de). Lithium enolates also add to nitroalkenes with lk topicity and, in certain circumstances, it is possible to alter product topicity by changing acceptor geometry. For example, the lithium enolate of cyclohexane adds to (E)-1-nitropropene to give predominantly the l-product while (Z)-1-nitropropene gives mostly the u-product.<sup>25</sup> Several rationalizations for this occurrence are given, including the possibility of a boat-like transition state or cycloaddition character. Using a Mukaiyama donor such as 1-(trimethylsiloxy) cyclohexane and dichloro(diisopropoxy) titanium as a catalyst, addition to

nitroalkenes gives products of ul approach--the opposite of enamine and lithium enolate addition topicity.<sup>26</sup> The major products are of l-configuration. Three intermediate cyclic nitronic esters were isolated and characterized. For this system, it is unknown why  $\text{TiCl}_4$  gives no diastereoselectivity, why three equivalents of  $(i\text{-PrO})_2\text{TiCl}_2$  are necessary, or why the stereochemical course of the reaction differs from previously known cases. Addition of  $\text{Sn(II)}$  enolates to nitroalkenes also appears to proceed through a ul approach to give products of l-configuration.<sup>27</sup> The  $\text{Sn(II)}$ -enolate of cyclohexanone reacts with  $\beta$ -nitrostyrene to give products of >86% de.

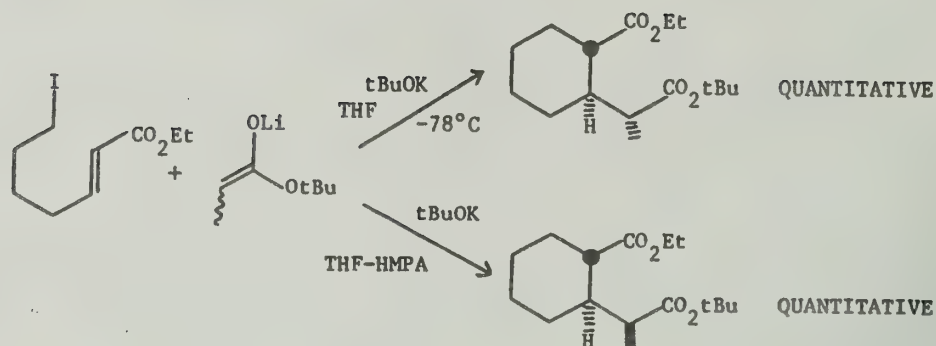
Scheme IX



Yamaguchi found that the lithium enolate of ethyl propionate add to ethyl crotonate through a ul approach regardless of the enolate geometry.<sup>28</sup> Hexamethylphosphoramide (HMPA) as an additive greatly increases the diastereoselectivity. When a lithium enolate derived from t-butyl propionate is used, the initial adduct can be diastereospecifically alkylated after treatment with  $\text{tBuOK}$  and methyl iodide. Using the same concept, Michael additions were followed by intramolecular alkylations to give five and six-membered rings.<sup>29</sup> This process leads to either a quantitative or nearly quantitative isolation of only one of the possible diastereomers. Moreover, alteration of the conditions leads to different diastereomers. With  $\text{tBuOK}$ , THF at  $-78^\circ\text{C}$ , the l,u-1,n ( $n = 4, 5$ ) product was isolated in quantitative yield. With  $\text{tBuOK}$ , THF-HMPA at  $-78^\circ\text{C}$  the u,u-1,n product was the only one isolated (Scheme X). Mulzer's work on Michael additions of  $\beta$ -lactone enolates to dimethyl maleate has shown that this system also exhibits diastereoselectivity.<sup>30</sup> The topicity of addition is ul with respect to the 3,3'- and lk with respect to the 3',4'-bonds. HOMO-LUMO interactions between donor and acceptor in addition to chelation of the cation are proposed to influence the diastereomeric outcome of the reaction.



Scheme X



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## 2,3-SIGMATROPIC RING EXPANSION OF 2-VINYLTTHIACYCLOALKANES: AN EFFICIENT ROUTE TO MEDIUM AND LARGE RING SYSTEMS

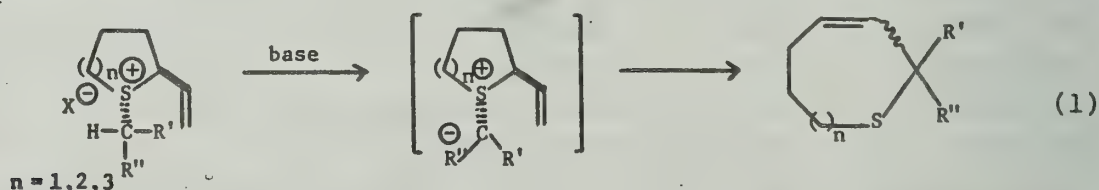
Reported by Kevin G. Pinney

March 20, 1986

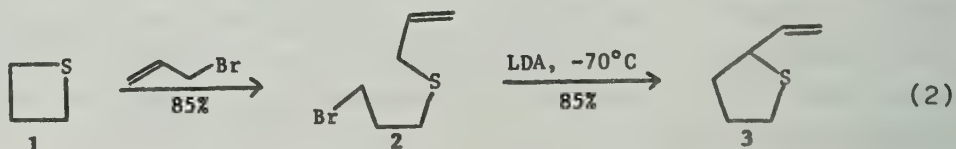
The first example of a sulfur-mediated 2,3-sigmatropic ring expansion of a cyclic sulfide was reported in 1975 by Vedejs and co-workers.<sup>1</sup> This rearrangement was previously known to occur with acyclic sulfides, and had precedent in the ring expansion of nitrogen ylides.<sup>2</sup> It was cleverly recognized that through application of sulfur extrusion chemistry, these ring expansions would allow rapid progress toward a variety of synthetically challenging macrocycles with varying functionality.<sup>3</sup>

### Preparation of 2-Vinylthiacycloalkanes

As illustrated in Equation 1, the 2,3-sigmatropic rearrangement results in ring expansion by three carbon units of the 5, 6, or 7-membered

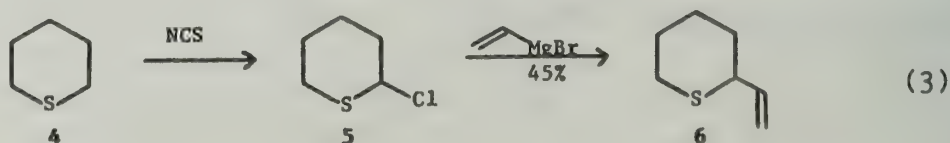


$\alpha$ -vinylthiacycloalkane precursors. The  $\alpha$ -vinyltetrahydrothiophene **3** is prepared from the commercially available cyclic sulfide **1** (Eq. 2). Treatment



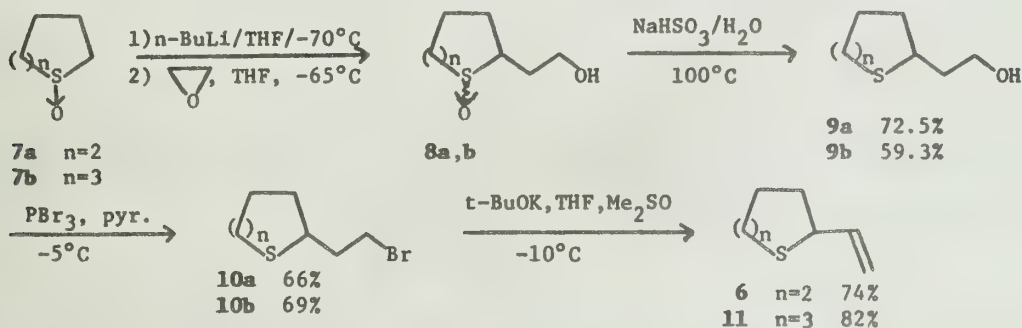
with allyl bromide affords the ring opened allyl sulfide **2** in high yield. Subsequent ring closure in the presence of lithium diisopropylamide (LDA) results in the desired tetrahydrothiophene **3**.<sup>1</sup>

A variety of strategies have been employed toward the synthesis of the 6-membered 2-vinylthiane.<sup>4</sup> In the most convenient route, pentamethylene sulfide **4** undergoes mono-chlorination selectively with N-chlorosuccinimide (NCS). Treatment of chlorosulfide **5** with vinylmagnesiumbromide yields the target **6** (Eq. 3). Fava and co-workers have reported the synthesis of 6- and



7-membered cyclic sulfides from the precursor sulfoxide **7** (Scheme I).<sup>5</sup> In this manner, the  $\alpha$ -vinylthiane **6** and the 7-membered homologue **11** are prepared in overall yields of 34.5% and 29.5%, respectively. This method is especially attractive as a means of preparing functionalized derivatives.

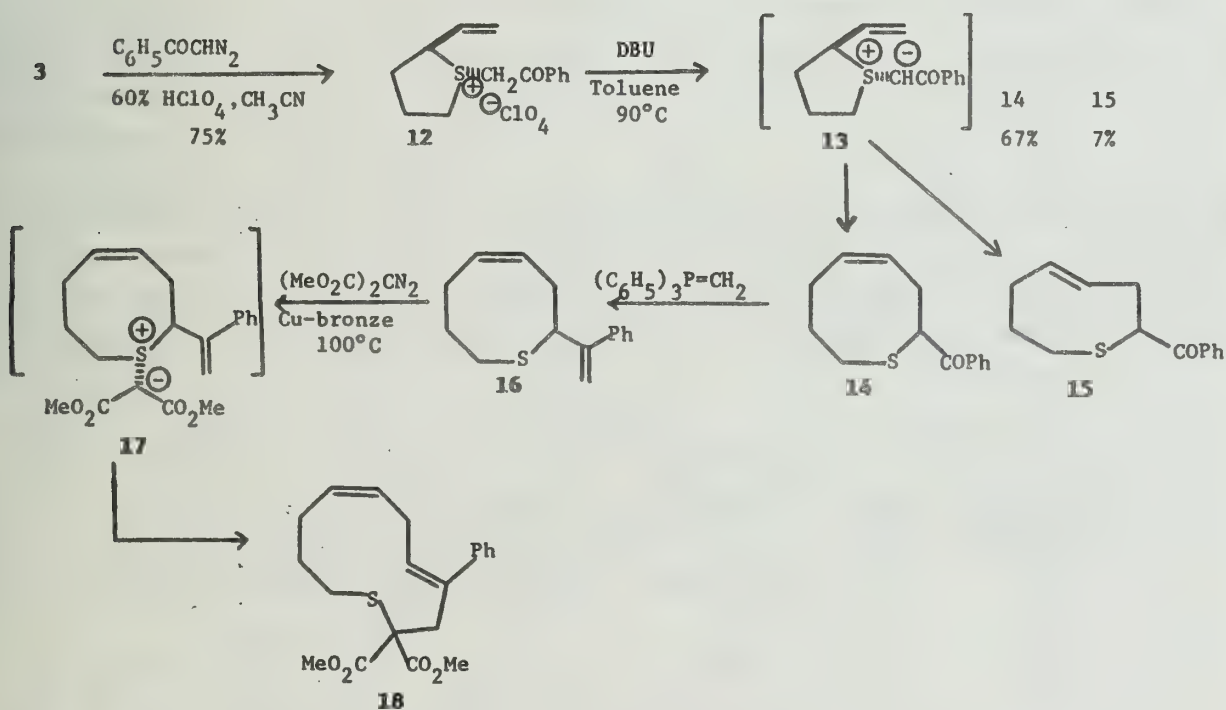
Scheme I



### Ring Expansion via Sulfur Ylides

The first reported example of the 2,3-sigmatropic ring expansion utilized the carbenoid route toward alkylation of the  $\alpha$ -vinyltetrahydrothiophene **3** (Scheme II).<sup>1</sup> Thus, the carbonyl stabilized sulfur ylide **13** undergoes a

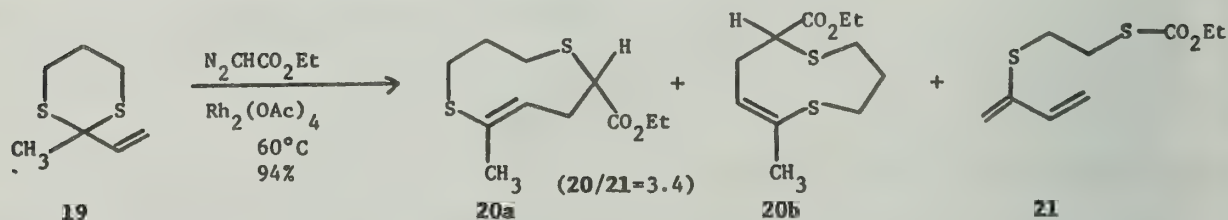
Scheme II



2,3-sigmatropic rearrangement to give a mixture of the cis (14) and trans (15) ring expanded products. A Wittig methylenation reaction on the cis isomer 14 forms the  $\alpha$ -vinylsulfide 16; subsequent alkylation via copper-bronze decomposition of dimethyldiazomalonate results in the 11-membered cyclic sulfide 18. Key features of this process include the highly stereoselective alkylation on sulfur to afford the corresponding trans sulfonium salt 12, and the inherent repeatability of the ring-expansion process.

While efforts to improve the copper catalyzed reaction were unsuccessful, more promising results were achieved using rhodium catalysis.<sup>3,6</sup> Doyle and co-workers demonstrated that 2-vinyl derivatives of 1,3-dithiane 19 give ring-expanded products in the presence of 1.0 mole%  $\text{Rh}_2(\text{OAc})_4$  and ethyldiazoacetate (Scheme III).

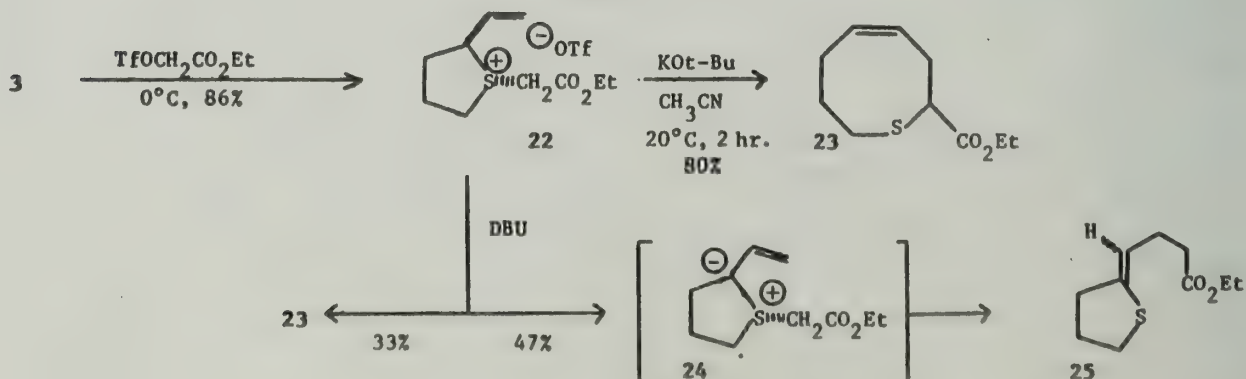
Scheme III



An alternative approach to in situ generation of stabilized sulfur ylides was attempted by treatment of  $\alpha$ -vinylsulfide 3 with ethylbromoacetate.<sup>7</sup> The only product observed, however, was the ring-opened sulfide resulting from nucleophilic attack of the bromide ion at the vinyl terminus.

The problem of nucleophilic attack was solved through the use of triflate alkylating agents.<sup>3,7</sup> Thus, treatment of the 5-membered sulfide 3 with  $\alpha$ -trifloxyethylacetate affords the triflate salt 22 in high yield (Scheme IV). There is no evidence of attack at the vinyl terminus by the non-nucleophilic triflate anion. A variety of bases were considered for the in situ ylide generation. Potassium t-butoxide ( $\text{KOt-Bu}$ ) gives the highest yield of the 8-membered ring as a single isomer (23). Treatment with 1,8-diaza-bicyclo[5.4.0]-undec-7-ene (DBU) gives 23 (33%) along with a mixture of vinyl sulfides 25 (47%), due most likely to equilibration of the exocyclic

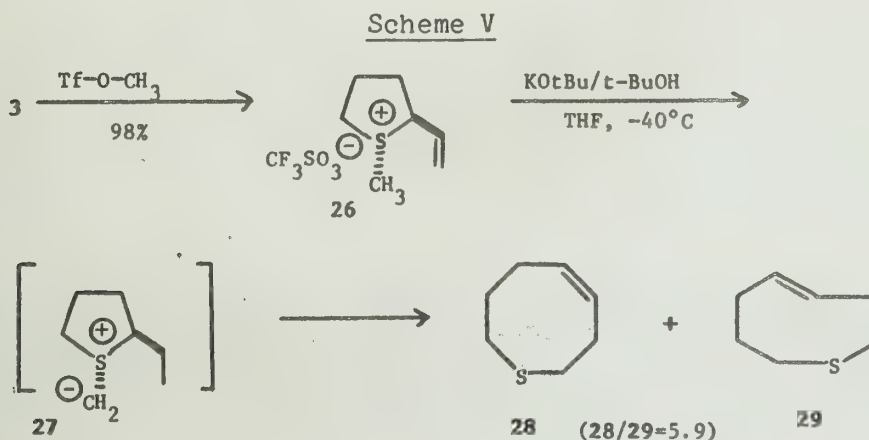
Scheme IV





ylide with endocyclic ylide 24. The triflate alkylation methodology was extended to the 6- and 7-membered  $\alpha$ -vinylsulfides 6 and 11, resulting in formation of the 9- and 10-membered ring-expanded products with yields in excess of 90%.<sup>6</sup>

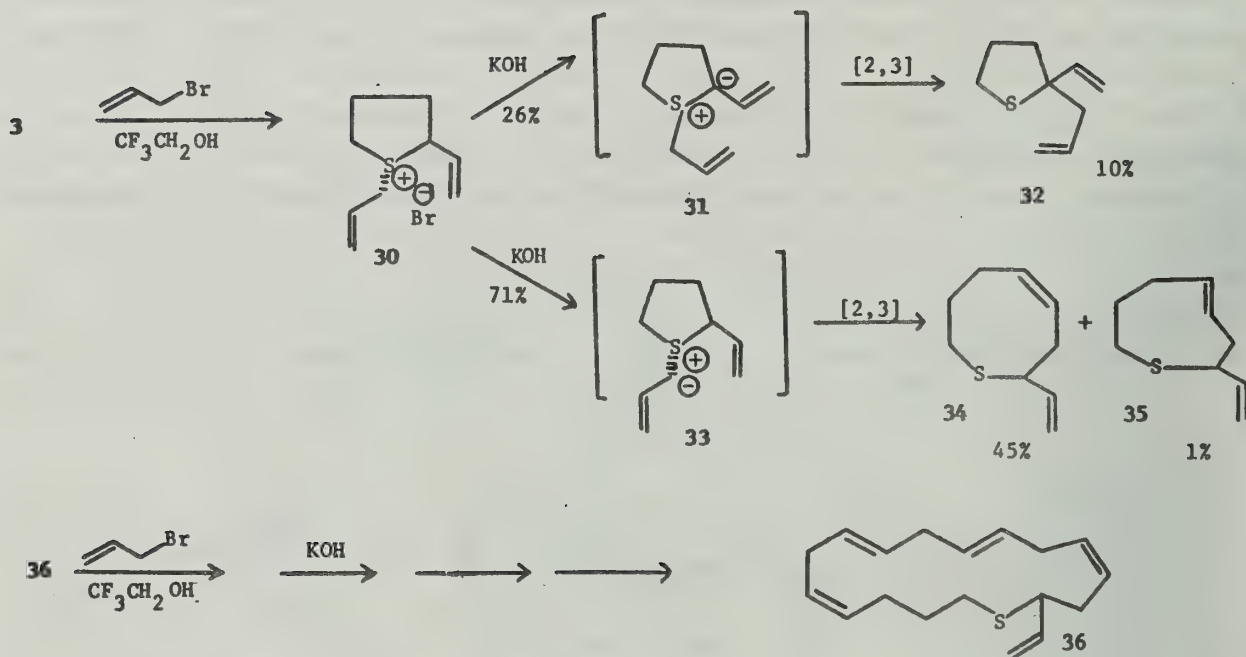
Fava and co-workers have extended the ring-expansion process to include nonstabilized sulfur ylides. Treatment of  $\alpha$ -vinylsulfide 3 with methyl trifluoromethanesulfonate affords the triflate salt 26 (Scheme V).<sup>5</sup> Subsequent



ylide generation with KOtBu followed by the 2,3-sigmatropic rearrangement results in a mixture of the cis (28) and trans (29) ring expanded products in an overall yield of 90%. The ring expansion is again seen to favor the cis olefin geometry in the 8-membered ring. This work has been successfully carried out on 5, 6, and 7-membered sulfonium salts with sulfur alkylated as methyl, ethyl and benzyl.<sup>5,9</sup> Yields are generally best using the hindered KOtBu as base.

An important aspect of this work centers on the repeatability of the 2,3-sigmatropic ring expansion process. This is illustrated by Vedejs in the formation of the 11-membered heterocycle 18 (Scheme II)<sup>1</sup> via the carbenoid route to the sulfur ylides, and again in the formation of a 12-membered heterocycle.<sup>10</sup> The repeatability is best illustrated by Schmid and Schmid utilizing allyl bromide as the alkylating agent.<sup>11</sup> Starting with the 5-membered  $\alpha$ -vinylsulfide 3, a series of four ring-expansions via the exocyclic allyl sulfur ylide affords the 17-membered sulfide 36 (Scheme VI). In each ring expansion, the  $\alpha$ -vinyl moiety remains in place and is ready for further expansion following sulfur alkylation. It is conceivable that this process could be extended to even larger ring systems.

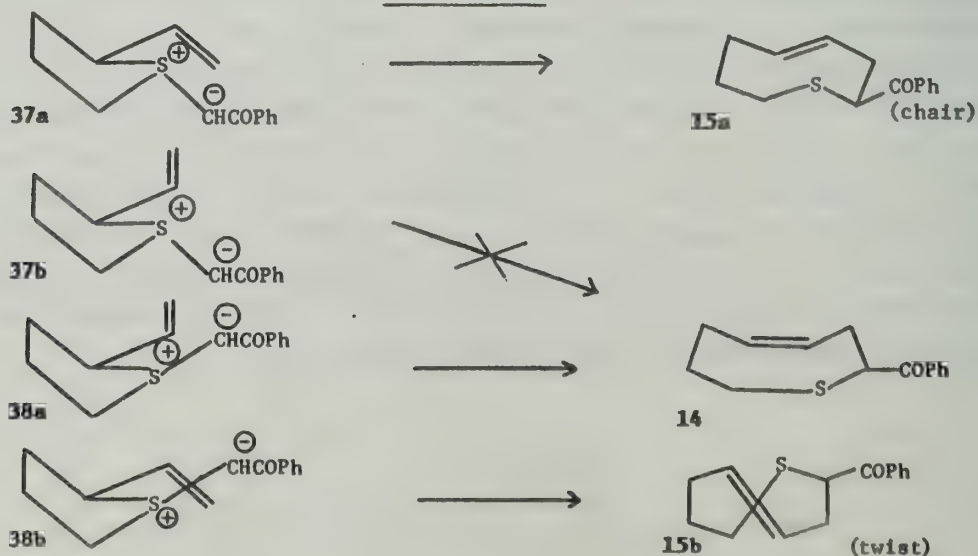
Scheme VI



Interconversion of Ylide Diastereomers

The 2,3-sigmatropic ring expansion appears to be stereoselective, with the geometry of the product olefin largely determined by the ring size.<sup>3,12</sup> Rearrangement to the 8-membered (Z) olefin **14** requires the cis disubstituted ylide **38** to achieve the 5-centered transition state favorable for the rearrangement (Scheme VII).<sup>1</sup> Since the sulfur alkylation is stereoselective

Scheme VII



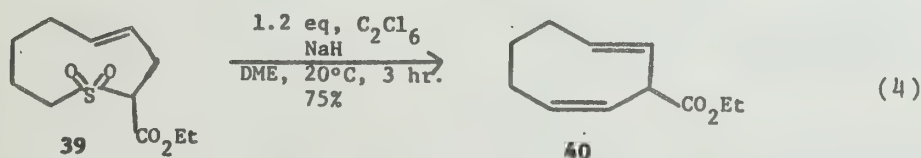
for the trans sulfonium salt which leads to the trans ylide **37**, an equilibration of the trans ylide to the cis ylide is necessary to explain the formation of the major isomer **14**. It is not possible to force the cisoid rotamer **37b** into a reasonable 5-centered transition state which might lead to the Z olefin **14**. Equilibration to the cis ylide **38**, however, would lead to the desired cis olefin through the cisoid vinyl rotamer **38a**.<sup>7</sup>

Three reasonable mechanisms for the interconversion have been proposed: a) reversible protonation-deprotonation through an endocyclic ylide; b) pyramidal inversion of sulfur; c) fragmentation of the allylic C-S bond and subsequent reclosure via a dipole or diradical species. The process most likely proceeds through equilibration with the endocyclic ylide, since diastereomer interconversion by pyramidal inversion at sulfur is too slow to compete, and indirect evidence exists for the formation of the endocyclic ylides.<sup>3,7</sup> Studies by Fava with non-stabilized sulfur ylides have given further support to the protonation-deprotonation pathway.<sup>12,13</sup>

The greater than nine-fold preference for Z-olefin (**14**) over E olefin (**15**) in the eight-membered ring system (Scheme II) contrasts markedly with the general trend for trans olefin formation in the 2,3-sigmatropic rearrangement of acyclic sulfides.<sup>14</sup> This most likely reflects a direct relationship to the strain energy of a trans olefin in an eight-membered ring. Rearrangement of  $\alpha$ -vinyl sulfides to nine-membered rings and larger again favors the E olefin product.<sup>3</sup>

### Sulfur Removal

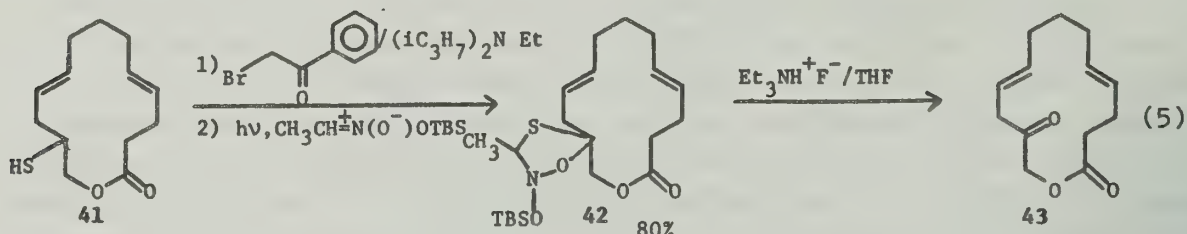
In order to convert the cyclic sulfides into likely target structures (lactones, carbocycles, etc.), methodology must be at hand for sulfur removal. Vedejs and co-workers utilized the classic Ramberg-Bäcklund sulfur extrusion method to convert the ring expanded sulfides into carbocycles. Treatment of cyclic sulfone **39** with hexachloroethane and excess sodium hydride results in formation, through the episulfone, of the cis, trans-cyclooctadiene ester **40** (Eq. 4).<sup>15,16</sup> Analogous sulfur extrusion from the 10-membered sulfone



homologue proceeds very slowly, generating the cyclononadiene in 33% yield. This methodology is utilized by Fava toward the synthesis of a [10.6]betweenane derivative.<sup>17</sup>

A novel approach to sulfur removal through sunlamp irradiation of phenacyl sulfides has been reported by Vedejs and Perry.<sup>18</sup> Using this technique, treatment of mercapto lactone **41** with phenacyl bromide and subsequent

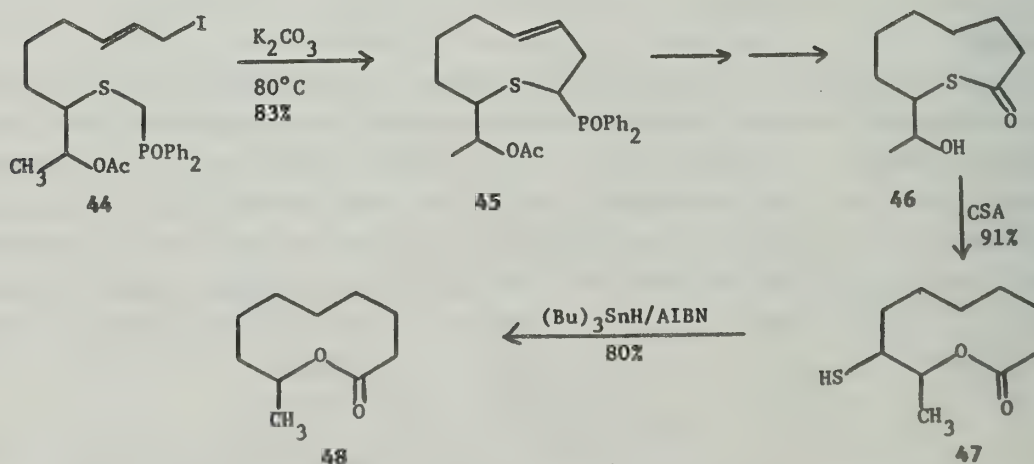
irradiation in the presence of thioketone scavenger  $\text{CH}_3\text{CH}=\text{N}(\text{O}^-)\text{OTBS}$ , affords **42** (Eq. 5). The 14-membered macrolide **43** is then formed upon treatment of **42** with  $\text{Et}_3\text{NH}^+\text{F}^-$ .



### Applications in Macrolide Synthesis

The sulfur mediated 2,3-sigmatropic ring expansion has been utilized as the key step in a variety of macrolide syntheses.<sup>3,19-23</sup> It was recognized that preparation of the initial sulfur heterocycle would be tedious for some of the highly functionalized systems often encountered in natural product synthesis. An alternative method for ylide formation was therefore developed utilizing intramolecular S-alkylation on an allylic iodide.<sup>24</sup> This method is especially convenient with complex substrates, since the intermediate sulfonium salts need not be isolated (Scheme VIII).

Scheme VIII

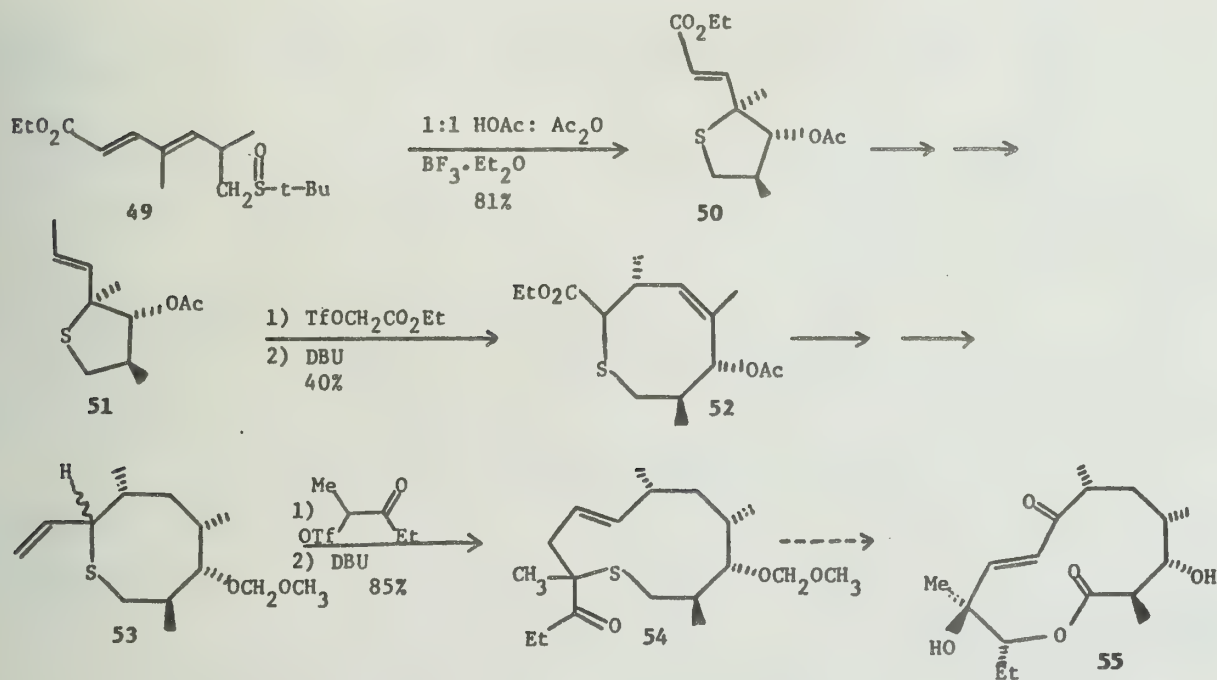


The most strategically promising route to the macrolides involves formation of a thiolactone from the ring-expanded cyclic sulfide followed by S-to-O acyl transfer.<sup>3</sup> This methodology is illustrated in Scheme VIII for the 10-membered macrolide, phoracantholide I.<sup>25</sup> Thiolactone **46** is converted to mercapto lactone **47** in the presence of camphorsulfonic acid (CSA). Sulfur removal with  $(\text{Bu})_3\text{SnH/AIBN}$  affords the target lactone **48**.



An elegant example of stereocontrol is illustrated by Vedejs and Mullins in their synthesis of a precursor to the 12-membered lactone, methynolide.<sup>20</sup> Treatment of the sulfenic acid derivative **49** with acetic acid-acetic anhydride in the presence of boron trifluoride etherate affords, as a single isomer, the cyclic sulfide **50** (Scheme IX) containing three asymmetric centers. Appropriate functional group manipulation results in the desired  $\alpha$ -propenyl tetrahydro-

Scheme IX



thiophene **51** which undergoes sulfur alkylation and subsequent ring expansion to the cis 8-membered sulfide **52** with stereocontrol at  $\text{C}_2$ ,  $\text{C}_3$ , and  $\text{C}_6$ . Following diimide reduction and formation of the vinyl moiety at C-7, a second alkylation and 2,3-sigmatropic ring expansion affords the 11-membered methynolide precursor **54** with the stereochemistry established by the initial cyclization of the sulfenic acid derivative **49** still intact. Conversion of the precursor **54** to methynolide **55** is currently under investigation.<sup>26</sup>

In conclusion, the sulfur-mediated 2,3-sigmatropic ring expansion has been shown to be a viable method for the preparation of medium to large membered ring systems with predictable stereochemistry. By incorporating methodology for S- to O-acyl transfer and subsequent sulfur removal, this technique has been utilized for the synthesis of a variety of complex macrolides.

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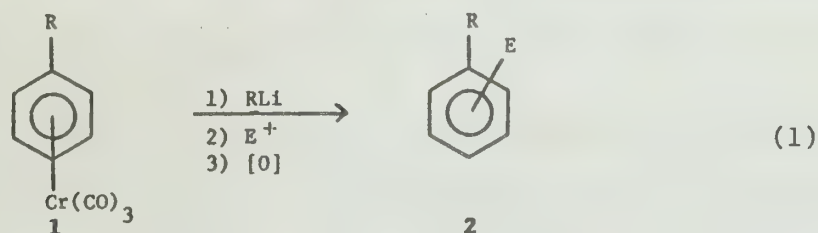
# METALATION OF ( $\eta_6$ -ARENE)TRICARBONYLCHROMIUM(0) COMPLEXES

Reported by Robert Lemieux

March 31, 1986

## Introduction

The functionalization of benzene and arene derivatives via tricarbonylchromium(0)  $\pi$ -complexes has been the subject of numerous studies over the past twenty years. Of importance have been studies of the alkylation of ( $\eta_6$ -halobenzene)tricarbonylchromium(0) by nucleophilic aromatic substitution and of the alkylation of ( $\eta_6$ -benzene)- and ( $\eta_6$ -arene)tricarbonylchromium(0) by addition-oxidation.<sup>1</sup> This review will focus on more recent advances in the field featuring the functionalization of ( $\eta_6$ -arene)tricarbonylchromium(0), **1**, by direct metalation with alkyl lithium bases under mild conditions and with moderate to high regioselectivity (Eq. 1).



## Preparation

The ( $\eta_6$ -arene)tricarbonylchromium(0) complexes are generally prepared in high yield by the reaction of hexacarbonylchromium(0) with the corresponding arene in refluxing benzene or dioxane for several hours.<sup>2</sup> The complexes are air stable, crystalline solids and the tricarbonylchromium moiety can be oxidatively removed under mild conditions in aqueous cerium(IV), by treatment with iodine or by simple exposure to sunlight in the presence of oxygen.<sup>2,3</sup>

## Structure

The crystal structures of a number of monosubstituted ( $\eta_6$ -arene)tricarbonylchromium(0) complexes have been resolved.<sup>4</sup> It was shown that the tricarbonylchromium moiety tends to adopt an eclipsed conformation as shown in Figure 1. Conformer **3** is observed for complexes bearing an electron-donating substituent R whereas conformer **4** is observed for complexes bearing an electron-withdrawing substituent R. These results were rationalized by Hoffmann et al. using molecular orbital arguments.<sup>5</sup> In solution, conformers **3** and **4** are thought to be in equilibrium and a study by Solladié-Cavallo found the relative proportions of **3** and **4** to be dependent upon the  $\pi$ -donor ability of



the substituent  $R^6$ . In agreement with the solid state results, **3** is found to be predominant in solution when R is electron-donating while **4** is predominant when R is electron-withdrawing.

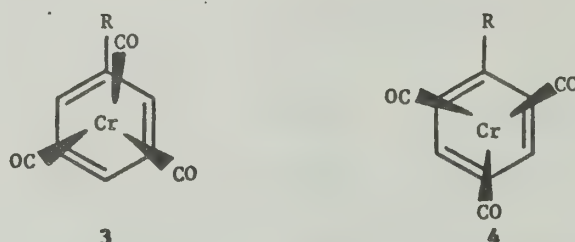


Figure 1

### Substituent Effect

The enhanced acidity of the arene ring protons upon coordination to a tricarbonylchromium moiety is believed to originate from the substantial electron withdrawing character of the chromium complex. This was demonstrated at an early stage when dissociation constant measurements showed that coordination to a tricarbonylchromium moiety causes a decrease in the  $pK_a$  of benzoic acid<sup>2</sup> by 0.98 and an increase in the  $pK_b$  of aniline<sup>7</sup> by 1.61. A study of Klopman and Calderazzo also showed that hydrolysis of the tricarbonylchromium complexes of various methyl benzoates proceed at rates 30 to 100 times faster than the hydrolysis of the free benzoates.<sup>8</sup> The electron withdrawing character of the tricarbonylchromium moiety was found to be comparable to that of a *p*-nitro group as the hydrolysis of ( $\eta_6$ -methyl benzoate)tricarbonylchromium(0) and methyl *p*-nitrobenzoate proceed at comparable rates. Theoretical support was provided by semi-empirical molecular orbital calculations reported by Carroll and McGlynn.<sup>9</sup> The calculated charge distribution in ( $\eta_6$ -benzene)tricarbonylchromium(0) (Fig. 2) shows a net transfer of electron density from the benzene ligand to the carbonyl oxygen. The positive character of the metal is believed to arise from more substantial  $\pi$ -back donation from the metal to the carbonyl groups relative to the forward  $\sigma$ -donation from the carbonyls to the metal. The measured dipole moment of 5.08 D for ( $\eta_6$ -benzene)tricarbonylchromium(0) was shown to be consistent with these results.<sup>10</sup>

The inductive constant  $\sigma_I$  and the resonance constant  $\sigma_R^0$  characterizing the total polar effect of a substituent have been measured for a phenyl group, free and coordinated with the tricarbonylchromium moiety.<sup>11</sup> It was shown that coordination causes the  $\sigma_I$  value of a phenyl group to increase from +0.10 to +0.21 while the  $\sigma_R^0$  value remains practically unaffected. These results led to the conclusion that coordination of benzene to a tricarbonylchromium moiety



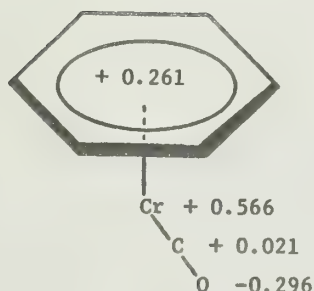
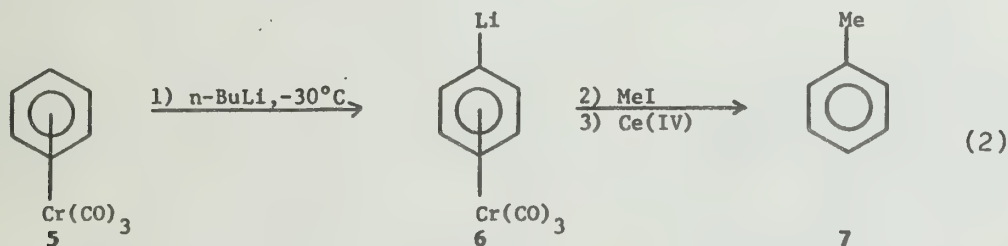


Figure 2

causes a net reduction in the electron density at the  $\pi$ -orbitals of the aromatic ring while the total  $\pi$ -electron density remains unaffected. This was shown to be consistent with the general theory of bonding in transition metal  $\pi$ -complexes<sup>12</sup> where mutual compensation between ligand to metal electron donation and back bonding from metal to ligand would result in an almost invariant  $\pi$ -electron density in the benzene ring upon coordination.

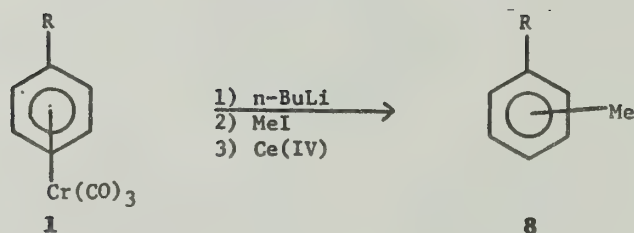
### Metalation

Early studies<sup>13</sup> showed that  $(\eta_6\text{-benzene})\text{tricarbonylchromium}(0)$ , **5**, can be metalated by treatment with  $n\text{-BuLi}$  at  $-30^\circ\text{C}$ . Trapping of the lithiated complex with methyl iodide followed by oxidative removal of the chromium moiety affords toluene, **7**, in 71% yield (Eq. 2). Trahanovsky identified **6** as the intermediate in the reaction by  $^1\text{H}$  NMR using phenyllithium and **5** as standards for comparison.<sup>13d</sup>



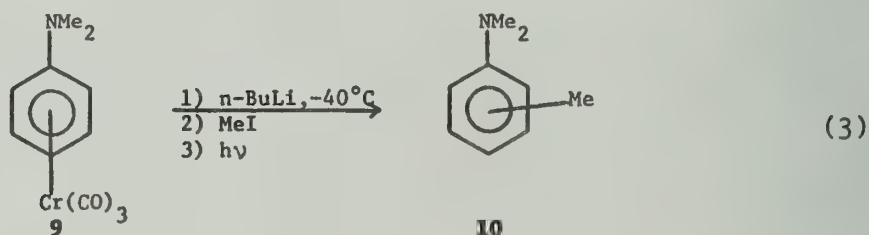
The direct ring metalation of alkyl substituted arenes is generally not efficient due to the preferential abstraction of benzylic protons. It was found however, that treatment of  $(\eta_6\text{-toluene})\text{tricarbonylchromium}(0)$  with  $n\text{-BuLi}$  followed by trapping with methyl iodide and oxidative decomplexation affords only 14% of ethylbenzene compared to 89% for the metalation of free toluene under similar conditions.<sup>13d</sup> As shown in Table 1, the coordination of alkylbenzenes with a tricarbonylchromium moiety leads to direct ring metalation in 54% to 80% yield but with poor regioselectivity.

Table I

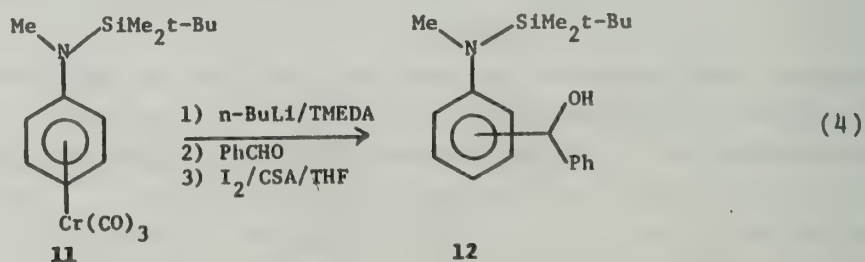


R	Alkylated product 8 (% yield)	
	$\alpha$	o,m,p
CH <sub>3</sub>	14	6,41,22
CH <sub>2</sub> CH <sub>3</sub>	1	5,49,26
C(CH <sub>3</sub> ) <sub>3</sub>	--	0,32,22

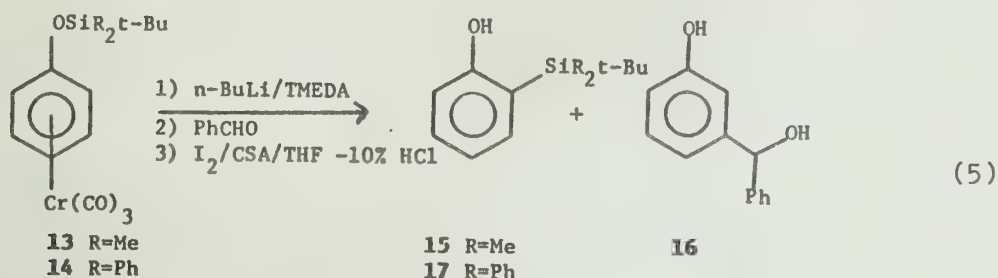
Using a similar reaction sequence, the metalation of ( $\eta_6$ -N,N-dimethylaniline)tricarbonylchromium(0), 9, with *n*-BuLi at -40°C has been reported to produce in a combined yield of 62% a mixture of N,N-dimethyltoluidines, 10, in a o:m:p ratio of 1.8:3:1 (Eq. 3).<sup>13d</sup>



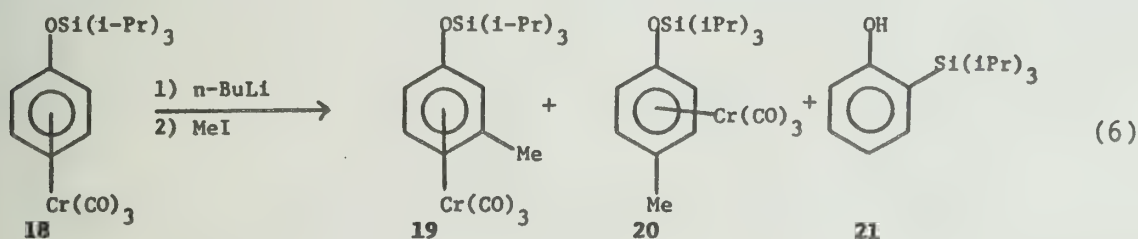
In contrast, uncomplexed N,N-dimethylaniline is known to metalate only at the ortho position upon treatment with *n*-BuLi in hexane under reflux.<sup>14</sup> Oishi has shown that the regioselectivity can be improved by increasing the bulkiness of the amine substituents.<sup>15</sup> Hence, the metalation of ( $\eta_6$ -N-t-butyldimethylsilyl-N-methylaniline)tricarbonylchromium(0), 11, with *n*-BuLi/TMEDA followed by trapping with benzaldehyde and subsequent decomplexation affords an isomeric mixture of the aniline derivative 12 in a m:p ratio of 49:1 whereas no ortho isomers are produced (Eq. 4).



The tricarbonylchromium complex of anisole was shown to undergo direct ring metalation with *n*-BuLi at the ortho position exclusively.<sup>13b</sup> An increase in bulk of the alkoxy group however, was found to suppress ortho metalation in favor of the meta position. Oishi reported that when (*η*<sub>6</sub>-*t*-butyldimethylsiloxybenzene)tricarbonylchromium(0), **13**, is treated with *n*-BuLi/TMEDA and the resulting species quenched with benzaldehyde, subsequent decomplexation affords the phenols **15** and **16** in 35% and 40% yield respectively<sup>15</sup> (Eq. 5). The formation of **15** is believed to occur via initial ortho metalation of **13**. The use of a bulkier *t*-butyldiphenylsiloxy group was found to suppress the yield of **17** to 19% while improving the yield of **16** to 48%.<sup>15</sup>



With the use of the even bulkier triisopropylsiloxy group, Widdowson was able to practically eliminate ortho metalation in favor of metalation at the meta position.<sup>16</sup> As shown in Eq. 6, the metalation of (*η*<sub>6</sub>-triisopropylsiloxybenzene)tricarbonylchromium(0), **18**, leads to the meta- and para-substituted complexes **19** and **20** in a 10:1 ratio and in 78% overall yield. Only trace amounts of **21** were isolated. The uncomplexed triisopropylsiloxybenzene was found to be unreactive under similar conditions.

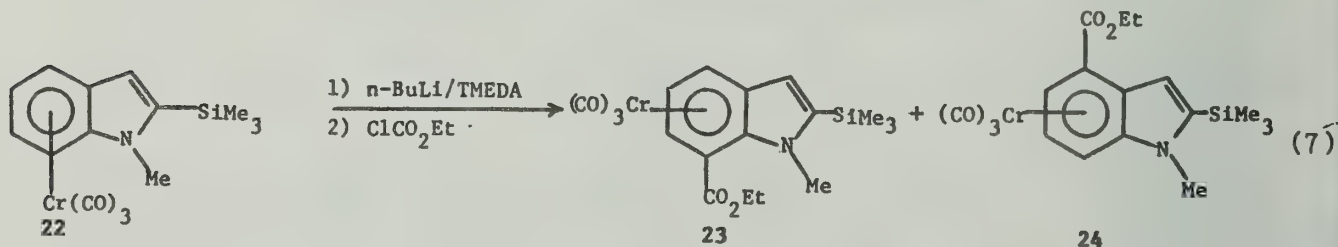


The tricarbonylchromium(0) complexes of fluoro- and chlorobenzene were also found to undergo metalation at the ortho position exclusively with *n*-BuLi under similar conditions.<sup>13b,d</sup>

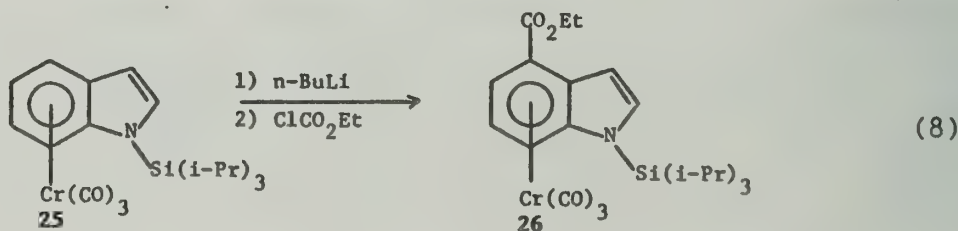
The unusual regioselectivity observed in the metalations of monosubstituted arene complexes may be rationalized by a general mechanism proposed by Trahanovsky<sup>13d</sup> in which initial coordination of the alkyl lithium base to the oxygen of one of the carbonyl ligands is believed to precede proton abstraction from the aromatic carbon nearest to the carbonyl ligand. Structural studies<sup>4,6</sup> which determined that arene complexes bearing an electron-donating substituent adopt eclipsed conformation **3** appear to be consistent with the

possibility that a directing effect of the carbonyl ligands eclipsed to the meta carbons would favor metalation at that position. In the case of N,N-dimethylaniline, anisole and halobenzene complexes, the occurrence of ortho metalation may be due to competition between the ortho-directing effect of the substituent and the meta-directing effect of the chromium moiety. The suppression of ortho-substitution in favor of meta-substitution by the use of bulkier substituents is consistent with this approach.

The metalation of N-methylindole with *n*-BuLi was shown a number of years ago to occur specifically at C-2.<sup>17</sup> More recently,<sup>18</sup> Widdowson found that, upon metalation with *n*-BuLi, trapping with ethylchloroformate and subsequent decomplexation, the protected ( $\eta_6$ -1-methyl-2-trimethylsilylindole)tricarbonylchromium(0) complex **22** affords a mixture of 7- and 4-ethoxycarbonyl derivatives **23** and **24** in a 4:1 ratio respectively and in 85% overall yield (Eq. 7).



Metalation at C-7 was shown to be suppressed in favor of metalation at C-4 when the N-methyl substituent was replaced by a bulkier N-triisopropylsilyl group,<sup>19</sup> as shown in Eq. 8. An X-ray structure of **22** was shown to be consistent with the mechanistic approach previously mentioned as two of the carbonyl ligands were found to be eclipsed with the C-4 and C-6 positions.<sup>18</sup>



More recently, Uemura investigated the effect of tricarbonylchromium coordination on the metalation of aromatic rings containing two ortho-directing groups at the 1,3-positions.<sup>20</sup>



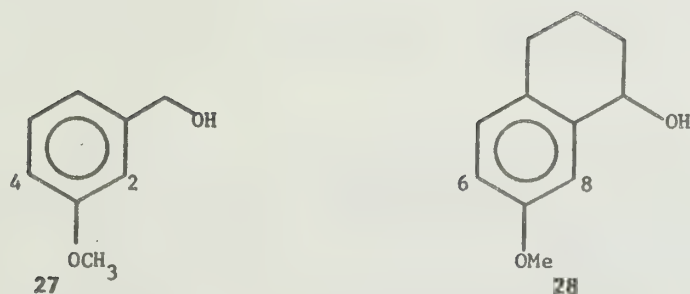
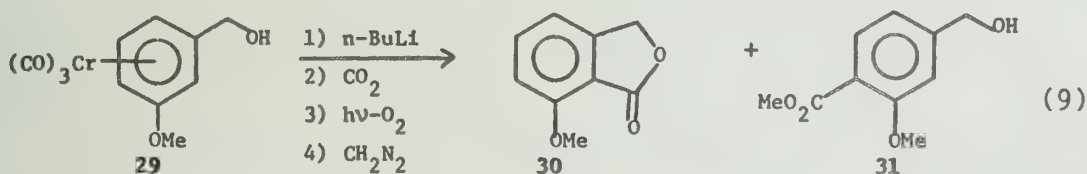
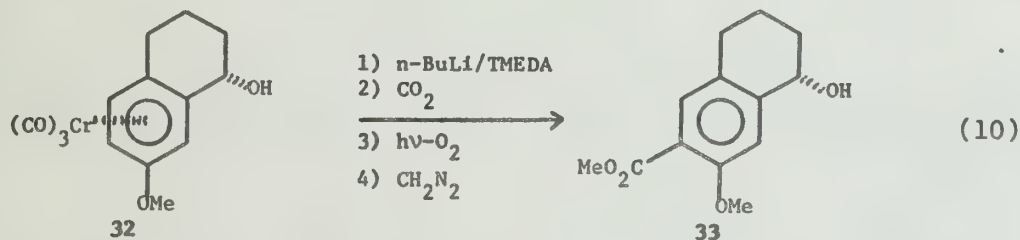


Figure 3

The lithiation of 3-methoxybenzylalcohol, 27, and its bicyclic analogue, 7-methoxy-1-tetralol, 28, is known to occur with high regioselectivity at the C-2 and C-8 positions respectively.<sup>21</sup> The metalation of the ( $\eta_6$ -3-methoxybenzylalcohol)tricarbonylchromium(0) complex 29, however, was found to occur mainly at the C-4 position instead of the C-2 position in a ratio of 3.4:1 (Eq. 9).



With the effect of coordination on the regioselectivity expected to be manifested more clearly by conformational fixation of the benzylic group, the metalation of the endo-( $\eta_6$ -7-methoxy-1-tetralol)tricarbonylchromium(0) complex, 32, with *n*-BuLi was found to occur exclusively at the C-6 position as shown in Eq. 10.



An X-ray crystal structure shows two of the carbonyl ligands to be eclipsed with C-6 and C-8.<sup>20b</sup> Uemura proposed that the lithiation is initiated by coordination of the alkyllithium to both the methoxy oxygen at the C-7 position and the carbonyl oxygen eclipsed to either the C-6 or C-8 position. The C-8 position is thought to be less susceptible to proton abstraction due to steric hindrance and electrostatic repulsion by the neighboring benzylic alkoxide anion on the incoming alkyl anion. The decreased regioselectivity

observed in the metalation of 31 is explained by the more flexible conformation of the benzylic alkoxide anion which allows metalation at C-2 to occur to some extent.

### Synthetic Applications

Applications of this novel methodology have been reported over the past five years. Semmelhack<sup>22</sup> has shown that lithiated tricarbonylchromium(0) complexes of anisole derivatives can be used as precursors in the synthesis of the quinone antibiotics alkavinone and frenolicin. Widdowson<sup>23</sup> also reported that the reaction of lithiated ( $\eta_6$ -fluorobenzene)tricarbonylchromium(0) with bifunctional electrophiles can lead via a multistep cycloaddition to the formation of 5-, 6- and 7-membered benzo-fused heterocycles. More recently, Uemura reported the use of the lithiated ( $\eta_6$ -7-methoxy-2-methyl-1-tetralol)-tricarbonylchromium(0) in a key step toward the synthesis of the anthracyclinone analogue deoxyrabelomycin.<sup>20c</sup>

### Conclusion

The coordination of various arenes to a tricarbonylchromium moiety thus allows mild functionalization of the arene nucleus via metalation with  $n$ -BuLi. Because the moiety can be introduced and removed from the aromatic nucleus in simple steps, the method provides an alternative mean of temporary altering the normal reactivity of aromatic systems. The metalation of  $\pi$ -arene chromiumtricarbonyl complexes is usually achieved with a regioselectivity not observed in the reaction of uncomplexed analogues and trapping of the lithiated intermediates affords functionalized arenes that are usually not available via electrophilic aromatic substitution.

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## LITHIUM CHELATION: EVIDENCE FOR DIRECTED METALATION

Reported by Anne Parson Wallin

April 3, 1986

Complexation of lithium reagents by heteroatoms is often proposed to explain both expected as well as curious and novel results such as the removal of a thermodynamically less acidic proton or unusual asymmetric induction.<sup>1</sup> For example, Miller and Saunders examined the deuterium isotope effects for the two enolates of 2-methyl-3-pentanone.<sup>2</sup> The isotope effects for the two enolates are drastically different. It does not seem reasonable that the addition of a single methyl for a rate determining deprotonation could have such a dramatic effect. Therefore, Saunders and Miller proposed that the proton removal is preceded by complexation of the lithium base to the ketone carbonyl.<sup>2</sup> There is, in fact, a large body of direct evidence and theoretical calculations documenting lithium's ability to complex strongly with heteroatoms including carbonyl oxygens, and this report will focus on these studies.

Strong support for lithium chelation is available from several ab initio studies of lithium ion, MeLi, and LiH with a wide variety of bases.<sup>3</sup> These associations are quite exothermic and are accompanied by a polarization of the electron density. The interactions are primarily ion-dipole, and a decreasing order of affinities is amides, ketones, and esters.

A wide variety of spectroscopic studies have examined the interaction of carbonyls and lithium salts. Calorimetry studies indicate that the interaction of dimethylformamide (DMF) with aqueous lithium salts is stronger than with water, NaCl (aq), or NaClO<sub>4</sub> (aq).<sup>4</sup> IR studies of amide carbonyls with lithium salts show a shift to lower frequency indicating chelation of the lithium to the oxygen.<sup>5</sup> In addition, new bands appear in the far-IR region which are attributed to cation-solvent vibrations.<sup>5,6</sup> The <sup>13</sup>C-nmr resonances of DMF and dimethylacetamide (DMA) show downfield shifts upon addition of LiCl, but the carbonyl carbons exhibit the largest shifts.<sup>7</sup> Examination of <sup>1</sup>H-nmr at various amide-salt ratios indicates that the coordination number of lithium is four.<sup>5,8</sup> Dynamic <sup>1</sup>H-nmr of DMF with lithium salts shows an increase in the rotational barrier of the amide bond again indicating complexation with the oxygen.<sup>9,10</sup> Crystal structures of N-methylacetamide (NMA) and LiCl complexes show a lengthening of the carbonyl bond and a shortening of the carbon-nitrogen amide bond.<sup>11</sup> Staley and Beauchamp have determined the lithium ion binding energies for a variety of  $\pi$  and n-donor bases in the gas phase.<sup>12</sup> The strongest evidence for lithium chelation in a metalation was the direct observation of sec-BuLi-amide complex using stopped flow IR.<sup>13</sup> Clearly complexation of a lithium reagent by a base and subsequent metalation of a center in its proximity is a reasonable and probable mechanistic explanation for "directed" metalations.



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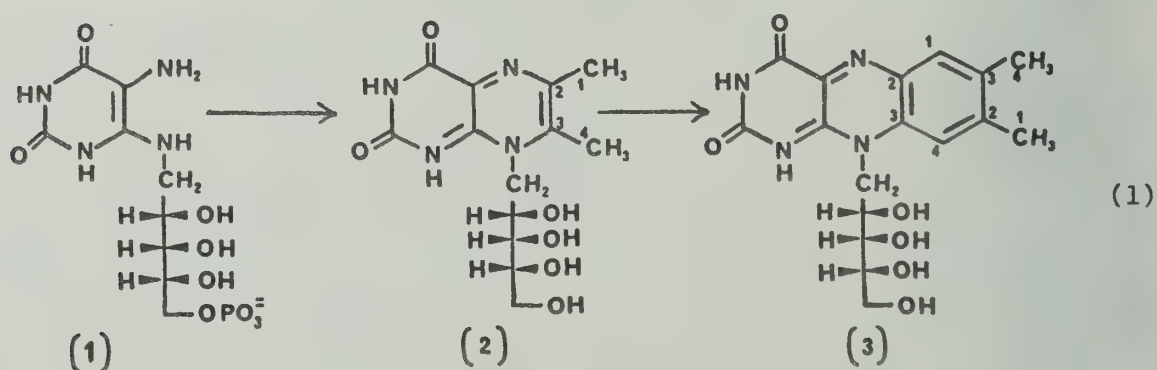
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## THE BIOSYNTHESIS OF RIBOFLAVIN

Reported by Andrew L. Staley

April 7, 1986

The biosynthesis of riboflavin (3) has been studied rather extensively during the last two decades using a variety of isotopic labeling methods, but certain key points have yet to be elucidated in detail.<sup>1</sup> Radiotracer studies with carbon-14 have established that the first obligatory step is the opening of the imidazole ring of GTP and the extrusion of formate.<sup>2,3</sup> Hydrolysis of the enamine and reduction of the ribose leads to 5-amino-6-(ribitylamino)-2,4-(1H,3H)-pyrimidinedione 5'-phosphate (1),<sup>4,5</sup> whose ribityl moiety has been shown to be retained from the original GTP precursor.<sup>2</sup> The addition of an as yet unidentified four-carbon unit to (1) leads to 6,7-dimethyl-8-ribityllumazine (2). Dismutation of two units of (2) results in the generation of one unit of riboflavin (3) and the regeneration of one unit of (1) with the regiospecificity shown in Equation 1.<sup>6,7</sup> Riboflavin can then be biosynthetically converted into the 5,6-dimethylbenzimidazole moiety of vitamin B<sub>12</sub>.<sup>8,9</sup>



The carbon-14 labeling studies suffered the usual lack of detail due to difficulties in degrading the products and randomization of the labels. Floss and Bacher have recently demonstrated the utility of carbon-13 labels in tandem with two-dimensional NMR techniques.<sup>10-16</sup> Their evidence points to a novel metabolic pathway in which the unidentified four-carbon unit is derived from the pentose pool via an intramolecular rearrangement. This involves the excision of C-4 and reconnection of C-3 and C-5 of an appropriate pentose unit.<sup>17-19</sup>

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# X-RAY CRYSTALLOGRAPHY OF METAL ENOLATES

Reported by Diane L. Ridout

April 10, 1986

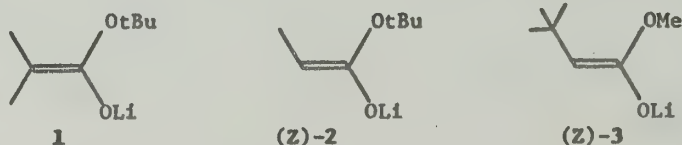
## Introduction

Metal enolates are possibly the most important class of nucleophiles for carbon-carbon bond formation in modern organic synthesis. While they are often referred to as carbanions or monomers, this is a gross oversimplification for these polar, associated organometallic species. A knowledge of the degree of aggregation, extent and nature of solvation, and the structure of metal enolates is required in order to understand their chemical behavior. The position of the metal may also be important in determining the stereo- and regiospecificity of reactions with electrophiles. X-ray crystallography is an excellent method available for obtaining data of this type.<sup>1</sup>

Lithium compounds engage in multicenter bonding. Dimers, trimers, and oligomers are common, the species actually formed being governed by steric effects. The degree of association frequently changes with temperature or solvent. The coordination sphere of the metal is often filled through interaction with electron rich molecules such as N,N,N<sup>1</sup>,N<sup>1</sup>-tetramethylethylenediamine (TMEDA), diethyl ether, or tetrahydrofuran (THF). There are many examples in which lithium coordinates to five or six donor atoms but since very few of the electrons are actually shared by the metal, the bonding has ion pair character.

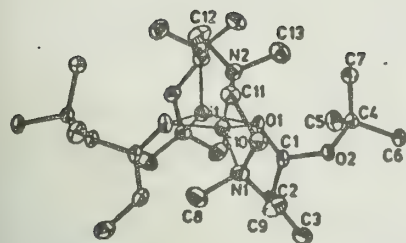
## Ester Enolates

Although the lithium enolates of esters were first isolated over ten years ago,<sup>2</sup> the X-ray structures for these simple compounds have only been reported recently.<sup>3</sup> The lithium enolates of t-butyl 2-methylpropionate (**1**), t-butyl propionate ((Z)-**2**), and methyl 3,3-dimethylbutanoate ((Z)-**3**) are shown below. Enolates **1** and (Z)-**2** are dimeric in the solid state with each lithium



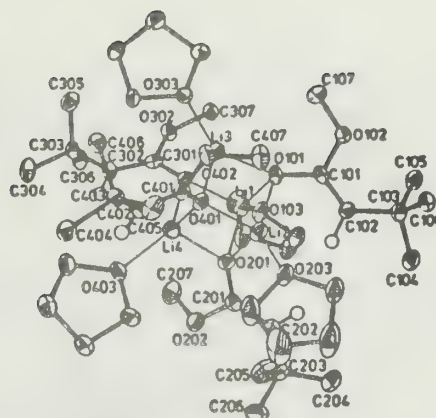
further coordinated by the two nitrogens of TMEDA (Figure 1, (Z)-**2**) whereas (Z)-**3** is tetrameric and each lithium is attached to one THF molecule (Figure 2). Figures 1 and 2 also confirm the stereochemistry of the kinetic enolates whose presence had previously only been deduced.





2-(Z)-2,2-TMEDA

Figure 1



4-(Z)-3,4-THF

Figure 2

One interesting point noted for the structures of 1, (Z)-2 and (Z)-3 is the fact that the carbon-oxygen bond is longer (1.30-1.32 Å, C-O-Li) than a typical carbonyl bond and shorter than the corresponding bond in a ketone enolate. Similarly the other carbon-oxygen bond (1.38-1.41 Å, C-O-R) is longer than the same bond in enol ethers. Seebach has therefore suggested that these structures represent the conversion of a trigonal center (ester enolate) into a diagonal center (ketene) and a leaving group (alcoholate) as shown in Figure 3.

The only other ester enolates which have been reported are those of pentakis(methoxycarbonyl)cyclopentadiene<sup>4</sup> and the Reformatsky reagent, derived from *t*-butyl bromoacetate.<sup>5</sup> The latter was found to be a cyclic dimer (Figure 4) with zinc almost tetrahedrally surrounded by one bromine, one carbon, and

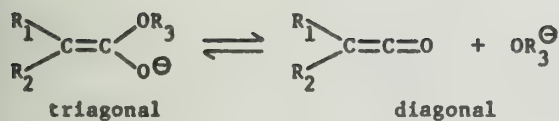


Figure 3

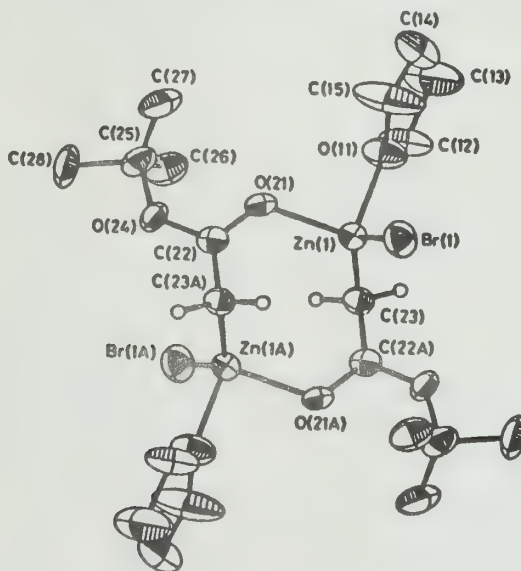


Figure 4

two oxygens. The authors believe that the dimer is also the reacting species in solution and propose two possible mechanisms for the reaction of this species with ketones (Figure 5). The first of these involves a four-membered

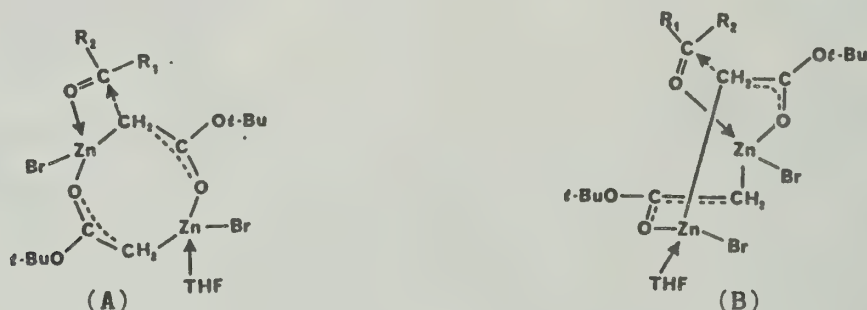


Figure 5

transition state (A) while the second involves a 6-center mechanism (B). Model studies show that there is more steric hindrance between the approaching carbonyl and the 8-membered ring in the 4-centered case than in the 6-center mechanism. On this basis the authors prefer the 6-center mechanism.

### Amide Enolates

Amide enolates such as lithium-8-(dimethylamino)-8-heptafulvenolate<sup>6</sup> and lithiated cyclohexanone dimethylhydrazone<sup>7</sup> have also been examined by X-ray crystallography. The latter structure was found to be an extended array with lithium coordinated to one anion in an  $\eta^4$  fashion and to the other in an  $\eta^1$  fashion (Figure 6). Lithiated 2-methylcyclohexanone dimethylhydrazone has a similar structure so the observed cis alkylations may be explained in terms of axial attack on the face opposite to the  $\eta^4$  bound lithium.

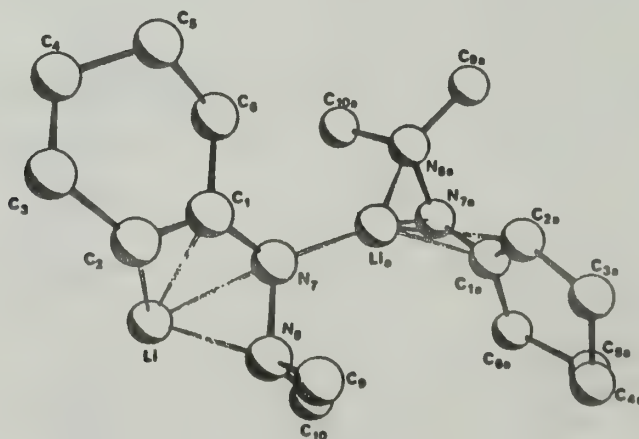
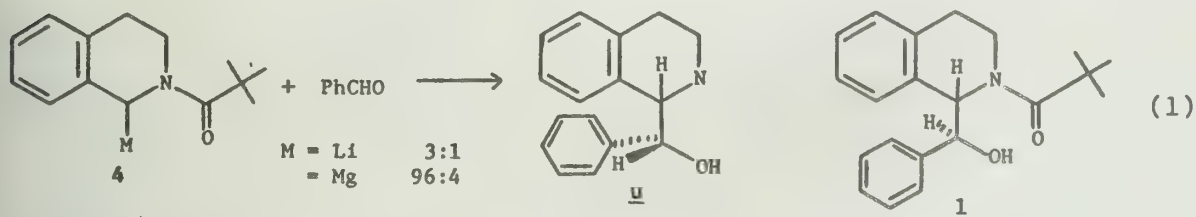


Figure 6

Although the lithium and magnesium derivatives of *N*-pivaloyl-tetrahydro-isoquinoline (**4**) are not officially enolates, they represent an example of how X-ray crystallography can be used to explain reactivity. More specifically, these derivatives were isolated in order to explain why **4** reacts preferentially with benzaldehyde to form the *u*-diastereomer with magnesium showing more selectivity (Equation 1).<sup>8</sup> Experimentally it was found that the lithium-enolate has tetrahedral



coordination while the magnesium-enolate is an octahedral complex. It has been proposed that the smaller angle of approach between the aldehyde and the magnesium derivative increases the steric interaction and in doing so raises the stereoselectivity of the reaction (Figure 7). Preference for formation of the *u*-diastereomer which is formed through a *ul*-transition state can be

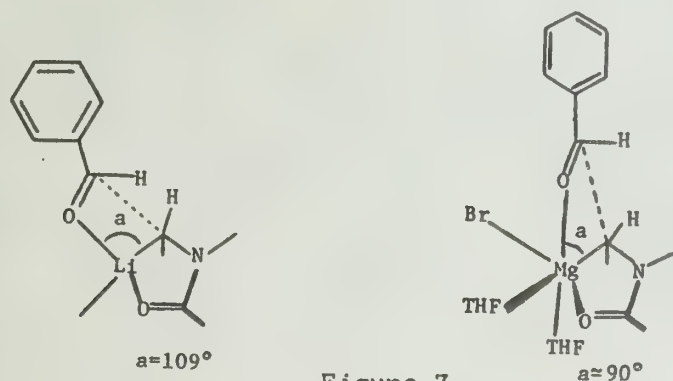


Figure 7.

explained in terms of less steric interaction between the phenyl ring with a pivaloyl methyl group (Figure 8).

### Ketone Enolates

By far the most work on X-ray crystallography of metal enolates has been done for ketones. The lithium enolate of pinacolone has been isolated although its structure appears to depend upon the method of formation. When the lithium diisopropylamide (LDA) used to prepare the enolate was recrystallized from THF prior to reaction with the ketone, a THF-solvated enolate tetramer was obtained (Figure 9).<sup>9</sup> However when unrecrystallized LDA was used to form the enolate, an unsolvated hexamer was obtained (Figure 10).<sup>10</sup> The C-O and C-C bond lengths

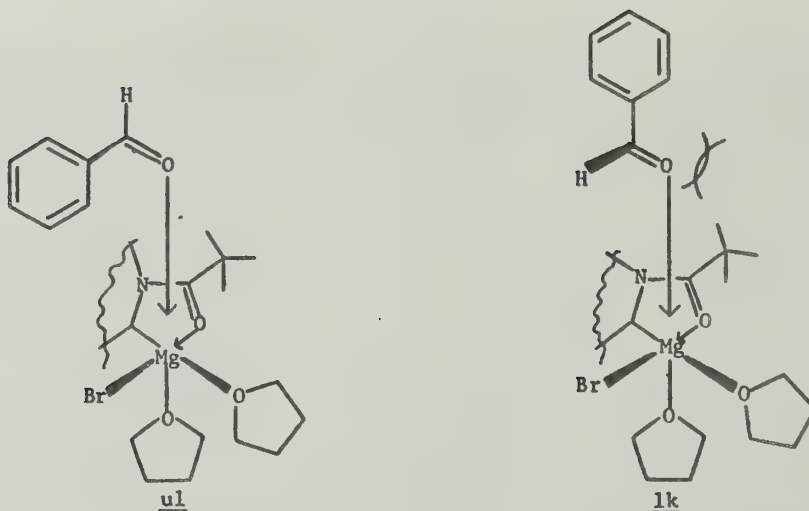


Figure 8

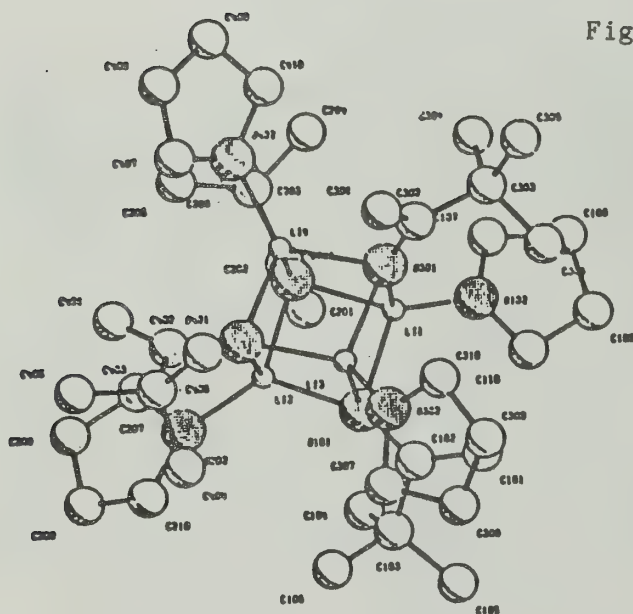


Figure 9

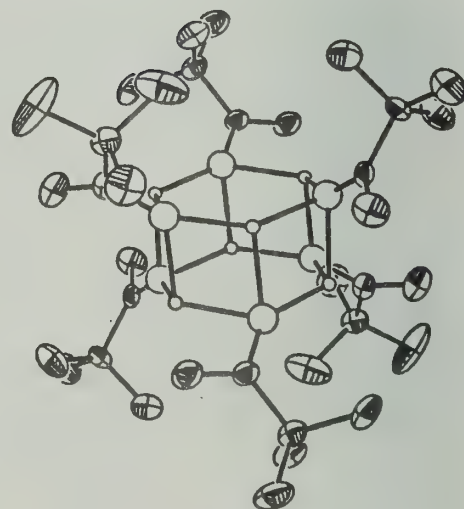


Figure 10

(1.34 Å and 1.33 Å, respectively) were found to be similar in the two aggregates. In the hexamer, the fourth coordination site on lithium appears to be filled through electron donation from the  $\pi$ -bond of the enolate. Seebach has discussed the mechanistic implications of these aggregates in terms of the aldol reaction (Figure 11).<sup>11</sup> The first step involves displacement of a solvent molecule from the lithium and replacement by the approaching electrophile. The carbon-carbon bond is next formed between the enolate and the electrophile after which the tetramer rearranges to include the new oxygen anion. Polar solvents or potent chelators would disturb this aggregate and so decrease C/O selectivity. The isolation of an aldol intermediate formed by the reaction of the lithium enolate of pinacolone with pivaldehyde (Equation 2) supports this proposed mechanism.<sup>13</sup>



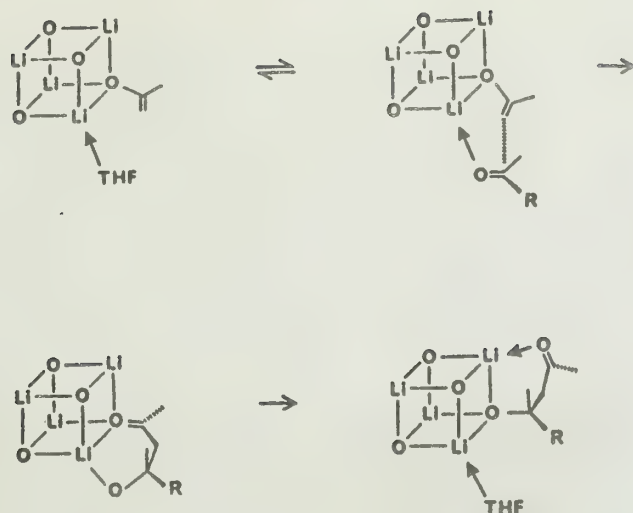
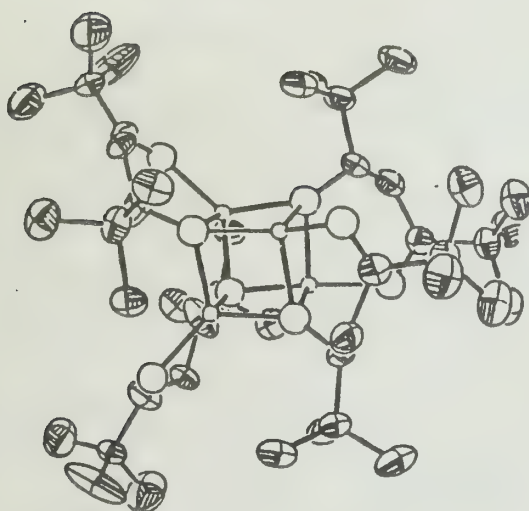


Figure 11



(2)

Recently, other metal enolates have been examined by X-ray crystallography. The sodium enolate of pinacolone was found to be a tetramer solvated by unenolized ketone while the potassium enolate is a THF-solvated hexamer.<sup>12</sup> Willard has suggested that these differences may account for the different reactivities in solution. The bromomagnesium enolate of *t*-butyl methyl ketone has also been studied. A dimeric ether-solvated structure was obtained.<sup>14</sup>

The X-ray structures of lithium cyclopentenolate,<sup>9</sup> methylcyclopentadienylsodium,<sup>15</sup>  $\alpha$ -(phenylsulfonyl)benzyl lithium,<sup>16</sup> and the anion 1,3-dilithiodibenzyl ketone have also been examined.<sup>17</sup> The 15-crown-5-sodium-ethyl acetoacetate enolates have been found to adopt the *u*-conformation with the metals above the plane of the crown by 0.9 Å and 1.05 Å, respectively (Figure 12).<sup>18</sup>



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# BOROLANES AND BORINANES: REAGENTS FOR ASYMMETRIC SYNTHESIS

Reported by Greg Anderson

April 24, 1986

## Introduction

The need for diastereo- and enantioselective reagents has become increasingly important as synthetic organic chemists contemplate complicated chiral targets.<sup>1</sup> In this regard, 1,3-dioxaborolanes **1** and **2**, and borolane **3** show amazingly high diastereo- and enantioselectivities in asymmetric alkylations and hydroborations. Additionally, homologations of dioxaborinane **4** have solved the long standing problem of asymmetric hydroboration of 1,1-disubstituted alkenes. In this abstract, the use of these similar reagents in asymmetric alkylations, hydroborations and natural products synthesis will be discussed.

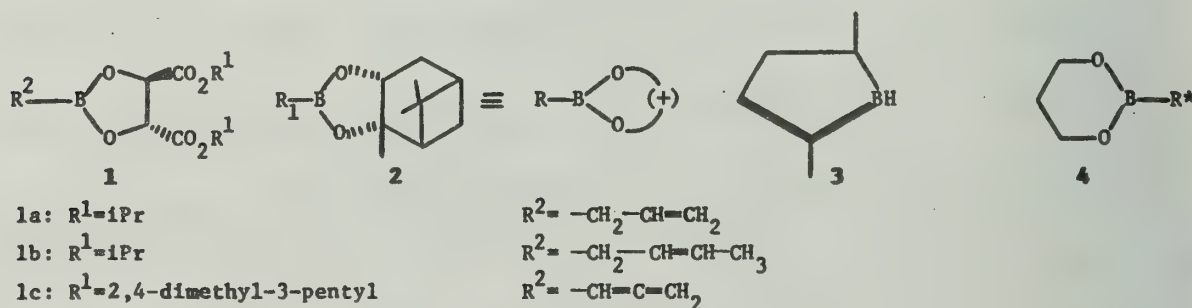


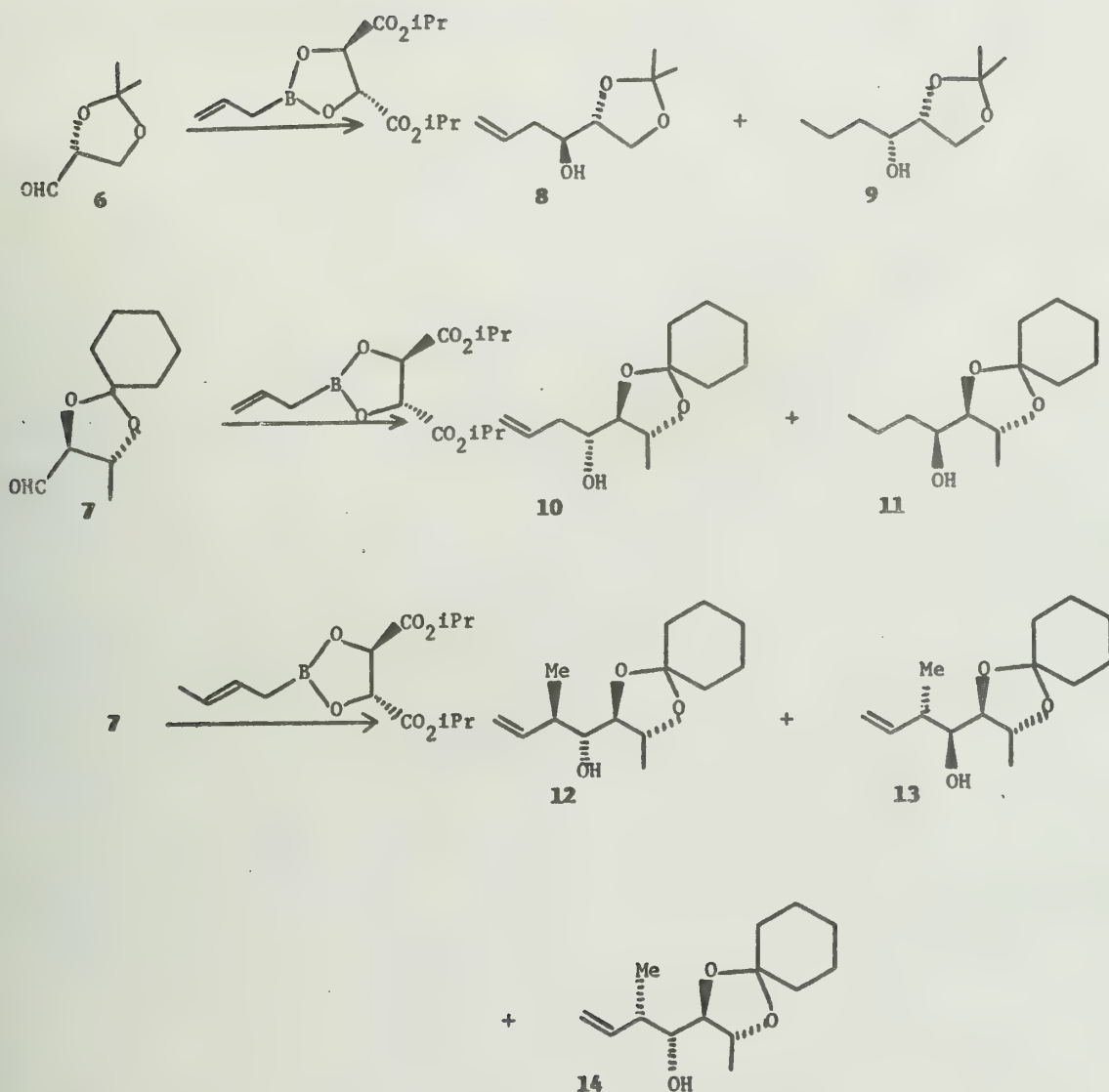
Figure 1

## Alkylations using 1,3-dioxaborolanes

Roush<sup>2,4</sup> and Yamamoto<sup>3</sup> have used a dioxaborolane of the general structure, **1**, to asymmetrically alkylate aldehydes. Roush allows **1a** to react with glyceraldehyde acetonide, **6**, and obtains a 96:4 preference for the erythro isomer, **8**.<sup>2</sup> The opposite diastereomer, **9**, can be obtained (8:92) by using the other enantiomer of diisopropyl tartrate (Scheme I). In a similar manner, acetonide **7** reacts preferentially (98:2) with **1a** to give the erythro isomer, **10**; however, the opposite diastereomer, **9**, cannot be obtained using the opposite enantiomer of diisopropyl tartrate.<sup>2</sup> Roush has also allowed dioxaborolane **1b** to react with **6** and **7** and obtained high selectivities.<sup>4</sup> By changing from (+)-**1b** (which gives an 88:4:8 ratio of **12** : **13** : **14** with **7**) to (-)-**1b**, one can obtain the other diastereomer, **13**, (4:93:3; **12** : **13** : **14**, Scheme I).<sup>4</sup>



Scheme I

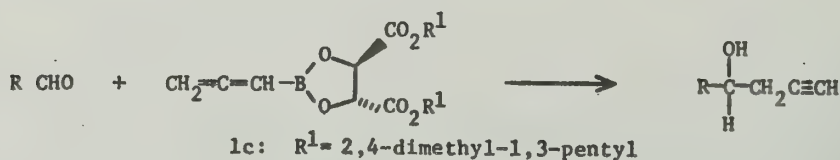


Additionally, **1a** gives high enantioselectivities with pivaldehyde (82%ee), cyclohexanecarboxaldehyde (87%ee), benzaldehyde (71%ee) and decanal (79%ee).<sup>2</sup> The facial selectivities of **6** and **7** without the chiral tartrate are moderate and always in favor of the erythro diastereomer (80:20, **6**; 90:10, **7**) when achiral pinacol allylboronate is used.<sup>5</sup>

Yamamoto has shown that **1c** reacts with several aldehydes to yield propargylic alcohols in >99%ee (Scheme II).<sup>3</sup> Reagent **1c** is formed by reaction of propargyl magnesium bromide with trimethyl borate.<sup>3</sup> Although the reaction is very successful in producing enantiomerically pure alcohols from various aliphatic aldehydes (hexanal (97%ee), cyclohexanecarboxaldehyde (99%ee) isovaleraldehyde (>99%), citronellal (99%ee)) only a moderate

enantioselectivity (79%ee) and low yield (<50%) are obtained with benzaldehyde; however other methods are available for aromatic aldehydes so that this method complements existing methodology.<sup>3</sup>

Scheme II



The enantioselectivities that Roush and Yamamoto obtain are comparable to or better than the results obtained by earlier workers using B-allyldiisopinocampheyl borane (80%ee)<sup>6</sup> or 3-phenyl-exo-2,3-bornanediols derivatives ( $\geq 70\%$ ee).<sup>7</sup>

Despite the similarity of the reagents and reactions, the transition states for the two reactions are thought to be different. Roush believes that the high facial selectivity in the reaction of **1a-b** with glyceraldehyde acetonide is a result of a heretofore unprecedented stereoelectronic interaction of the lone pairs of oxygen (Figure 2) on the aldehyde and tartrate

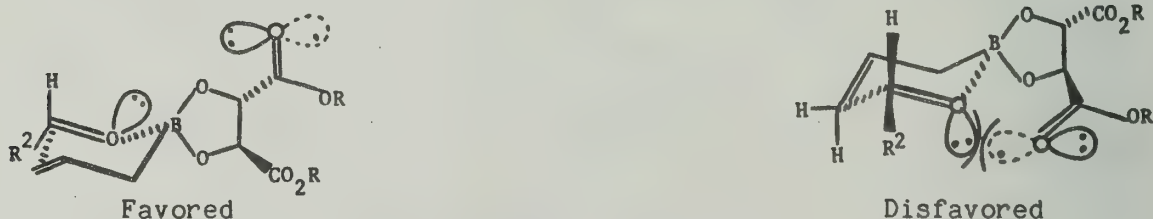


Figure 2

ester.<sup>2</sup> Yamamoto believes merely steric interactions of the tartrate ester with alkyl portion of the aldehyde gives rise to the observed enantioselectivity in the reactions of dioxaborolanes **1c-d** (Figure 3).<sup>3</sup>

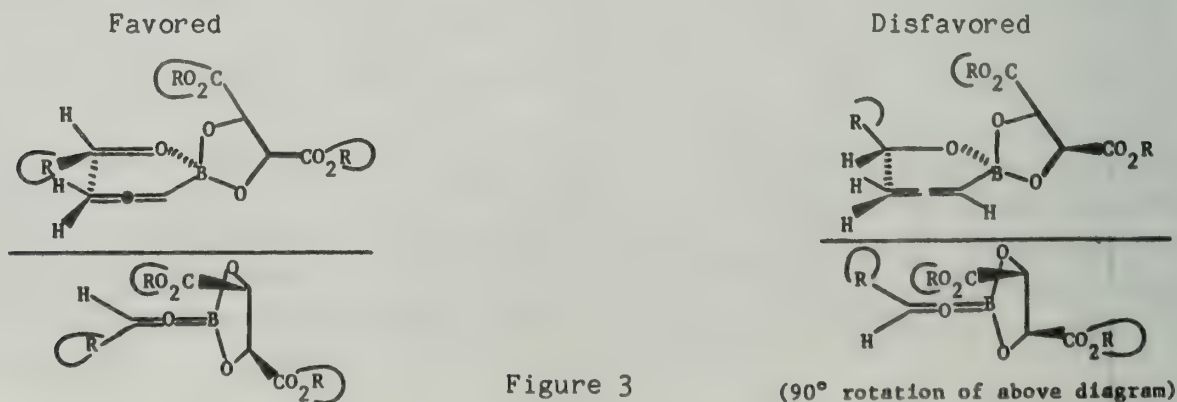


Figure 3

### Asymmetric Hydroboration with Borolane 3

Masamune has recently reported the use of chiral borolane 3 for the asymmetric hydroboration of several alkenes.<sup>8</sup>

All but 1,1-disubstituted alkenes (Type I alkenes, Figure 4) undergo asymmetric hydroboration in greater than 95% ee. As shown in Table I, 3, which is generated in a 9 step sequence beginning from dibromohexane, gives exclusively the S configuration with a variety of Type II-IV (Figure 4) alkenes

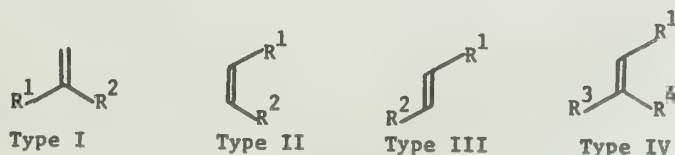


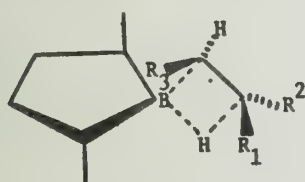
Figure 4

in 60-90% yield. Isopinocampheyl borane ( $\text{IpcBH}_2$ ) or other similar reagents have not achieved the degree of enantioselectivity for the S alcohol that is

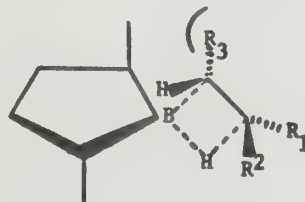
Table I. Asymmetric Hydroboration with reagent 3<sup>8</sup>.

Starting Material	Product	Yield (%)	% ee	% ee lit <sup>8</sup>
		75	97.6 (S)	99 (R) 86 (S)
		71	99.5 (S)	73 (S)
		90	97.6 (S)	70 (R) 53 (S)
		60	95.6 (S)	77 (S)

observed with 3 although Brown has recently reported that the enantiomeric purity of various Type II-IV alkenes can be improved significantly by fractional crystallization.<sup>9</sup> Masamune proposes that the high enantioselectivities can be rationalized by the steric interaction of the methyl groups on the borolane with the alkyl substituent of the alkene (Figure 5).<sup>8</sup>



Favored

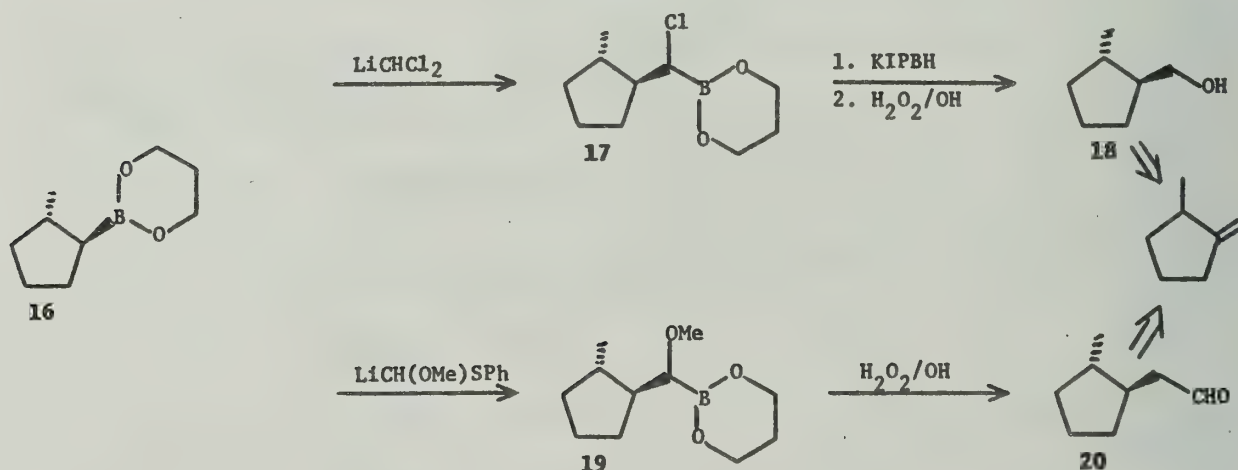


Disfavored

Figure 5

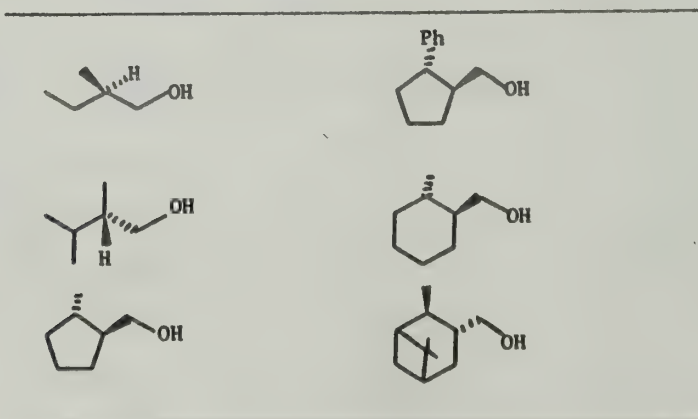
**Hydroboration of Type I alkenes.** Brown has recently reported a solution to the problem of asymmetric hydroboration of Type I alkenes.<sup>10,15,20</sup> Brown has shown that chiral boronic esters (e.g., **16**, 99%ee) prepared from alkenes can be homologated to  $\beta$ -chiral boronic esters (e.g. **17**, **19**) with complete retention of stereochemistry by treatment with  $\text{LiCHCl}_2$ <sup>10,15</sup> or  $\text{LiCH(OMe)SPh}$ .<sup>20</sup> The  $\alpha$ -chloroboronic ester, **17**, derived from reaction of  $\text{LiCHCl}_2$  is reduced to the  $\beta$ -chiral alcohol, **18** (i.e., the chirality is  $\beta$  to the alcohol), upon treatment with  $\text{K(i-PrO)}_3\text{BH}$  (KIPBH) followed by  $\text{H}_2\text{O}_2/\text{OH}^-$ .<sup>15</sup> The  $\alpha$ -methoxy boronic esters derived from reaction of  $\text{LiCH(OMe)SPh}$  are reduced to the aldehyde, **20**, upon treatment with  $\text{H}_2\text{O}_2/\text{OH}^-$  (Scheme III).<sup>20</sup> Effectively, this

Scheme III



transformation constitutes an asymmetric hydroboration of Type I alkenes. Various  $\beta$ -chiral alcohols that Brown has prepared are shown in Table II. Additionally, these  $\beta$ -boronic esters can be homologated and reduced to yield  $\gamma$ -chiral alcohols.

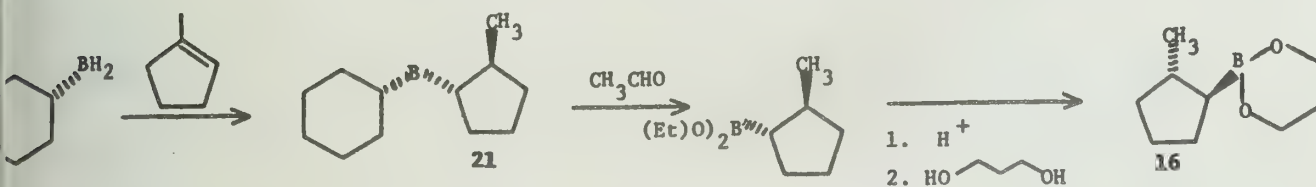
Table II. Various alcohols prepared by homologation with  $\text{LiCHCl}_2$  (yield: 60-90%, >99%ee)<sup>15</sup>





The starting boronic esters are obtained by hydroboration of the corresponding alkene. For example, 2-(2-methylpentyl)-1,3,2-dioxaborinane, **16**, is prepared by first subjecting 2-methyl-cyclopentene to hydroboration with  $\text{Ipc}_2\text{BH}$  and then treating with acetaldehyde. The resulting diethyl-2-(2-methylcyclopentyl) boronate ester can be hydrolyzed with acid, and reesterified with propanediol (Scheme IV).<sup>22</sup>

Scheme IV

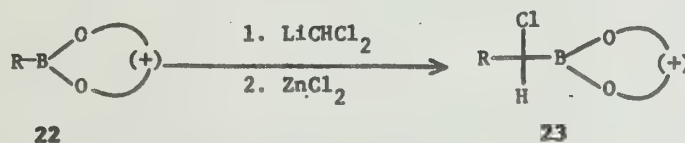


The high degree of enantiomeric purity of the starting boronic esters used to make the alcohols in Table II results from recrystallization of the intermediate borane (e.g., **21**).<sup>9</sup>

#### Diastereomerically Pure $\alpha$ -Chloroboronic Esters

While Brown has been interested in the synthesis of  $\beta$ -chiral alcohols or aldehydes using  $\text{LiCHCl}_2$  or  $\text{LiCH(OMe)SPh}$ , Matteson finds that diastereomerically pure  $\alpha$ -chloroboronic ester, **23a-e**, can be obtained from (+)-pinanediol boronic esters, **22a-e**, after homologation with  $\text{LiCHCl}_2$  (Table III).<sup>11-14,19</sup>

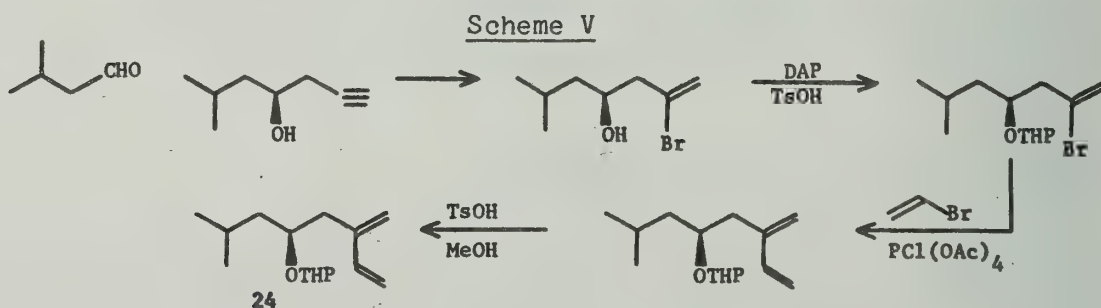
Table III. Diastereoselectivity of the homologation of (+)-pinanediol boronic esters, **22a-e**.<sup>19</sup>



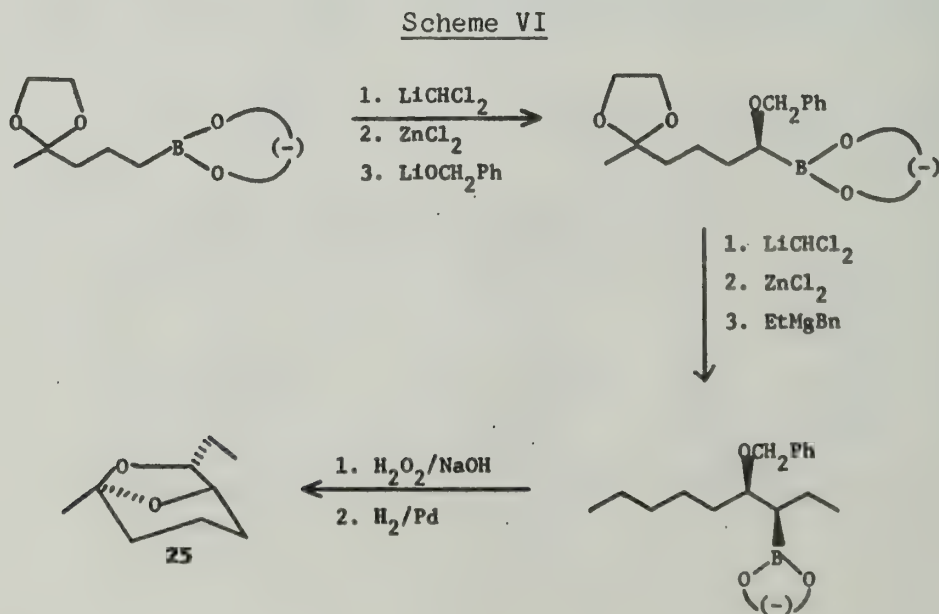
	R	Diastereoselectivity (%)		[Yield (with $\text{ZnCl}_2$ , %)]
		no $\text{ZnCl}_2$	with $\text{ZnCl}_2$	
a	iPr	--	99	87
b	Me	74	95.7	83
c	Bu	90	98.7	92
d	iBu	88	99.5	89
e	$\text{PhCH}_2$	92.5	99.5	99

As the comparison in Table III suggests,  $\text{ZnCl}_2$  is required in most cases to prevent epimerization by chloride of the  $\alpha$ -chloroboronic ester. Displacement of these  $\alpha$ -chloro boronic esters with  $\text{CH}_3\text{MgBr}$ ,  $\text{Li}(\text{Si}(\text{CH}_3)_4)_2$  or  $\text{CH}_3\text{CH}_2\text{MgBr}$  gives good yields with complete inversion of stereochemistry.<sup>11-14,19,23</sup>

**Natural Products Synthesis with Dioxaborolanes.** Both Roush<sup>17</sup> and Wuts<sup>18</sup> have used the stereoselectivity of dioxaborolanes in ionophore and carbohydrate synthesis. Also, Yamamoto has reported the enantioselective synthesis of (-)-iposenol, **24**, using dioxaborolane **1d** (Scheme V). Isovaleraldehyde reacts with dioxaborolane, **1d**, to give greater than 99%ee (78% yield) of the homopropargylic alcohol, **20**. This was carried onto (-)-iposenol by known chemical reactions.<sup>3a</sup>



Matteson has prepared exo-brevicomine **25** using the  $\text{LiCHCl}_2$  homologations (Scheme VI).<sup>19</sup> In addition to showing the versatility of repeated homologations for chiral synthesis, Matteson also shows the compatibility of a ketal with the homologation conditions.



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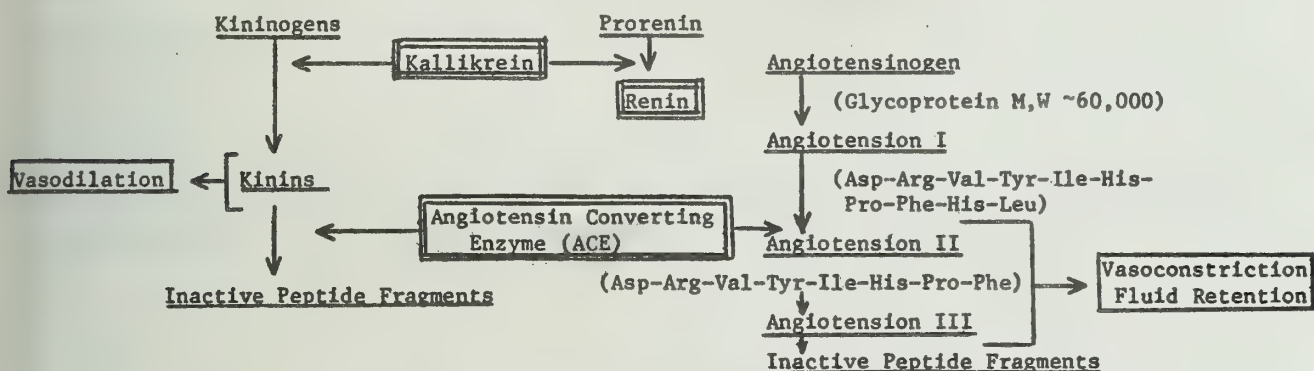


# ANGIOTENSIN CONVERTING ENZYME INHIBITORS

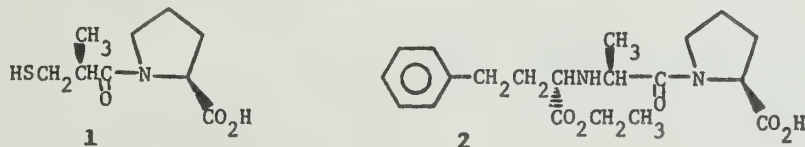
Reported by Keith C. Bible

April 28, 1986

Inhibitors of angiotensin converting enzyme (ACE) are important, clinically effective compounds receiving increasingly more utilization in the treatment of hypertension and congestive heart failure.<sup>1-4</sup> As seen in Scheme I, ACE plays an important role in the hormonal system which regulates blood pressure and intravascular volume/diuresis. The clinical utility of ACE inhibitors has been largely attributed to a blockade of these pathways.<sup>4,5</sup>



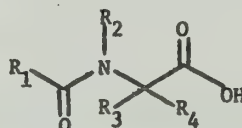
Two ACE inhibitors, captopril 1 and enalapril 2, are currently available for use by U.S. physicians. Both drugs are readily orally absorbed, have relatively minor and/or rare side-effects, and are first or second line drugs for the treatment of essential hypertension.<sup>3,4</sup> Both compounds are also useful in the treatment of congestive heart failure which is refractory to vigorous digitalis and diuretic therapy (although only captopril has been FDA approved for this indication).<sup>1,2</sup>



To date, several hundred ACE inhibitors have been synthesized by chemists.<sup>6-12</sup> Strategies for the development/discovery of these compounds have included: 1) the use of analogy to similar enzyme systems;<sup>13</sup> 2) the design of compounds with good "fit" for proposed ACE receptor site geometry;<sup>13-14</sup> 3) the testing of natural products (e.g., fermentation broths, peptide isolates) for ACE inhibition;<sup>15-18</sup> and 4) the synthesis of heteroatom analogues, chain length variations, cyclized derivatives, R group variations and stereochemical alterations of known ACE inhibitors.<sup>6-12</sup> Further, computerized conformational analysis and active site modeling have recently

been utilized to provide additional insight into ACE inhibition and assist in drug design.<sup>19</sup>

With few exceptions, ACE inhibitors are of the following general structure, where all 4 R groups are subject to considerable variation. Active compounds differing from this basic structure, have, in general, been discovered via screening of natural products for ACE inhibition - and not by other utilized ACE inhibitor design strategies.



Although additional research into different and/or more potent ACE inhibitors will undoubtedly lead to a better understanding of ACE enzyme/substrate interactions, it will probably not yield compounds of greater clinical utility than those already available. Nevertheless, research into angiotensin II receptor blockade and into renin inhibitors has received relatively little attention in the literature, and may indeed yield important new drugs.

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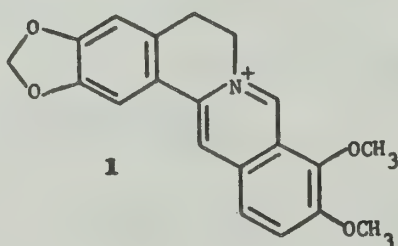
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## THE BIOSYNTHESIS OF BERBERINE AND PROTOBERBERINE ALKALOIDS

Reported by John Carney

May, 1, 1986

One of the largest classes of isoquinoline alkaloids comprises compounds based on the protoberberine nucleus, where berberine **1** is the prototypical compound. A large number of hypotheses on the biosynthesis of protoberberines based on *in vivo* experiments have been advanced.<sup>1</sup> Many details of the pathway, however, have only recently been delineated by experiments involving enzymes isolated from cell suspension cultures of genera which produce protoberberine alkaloids.



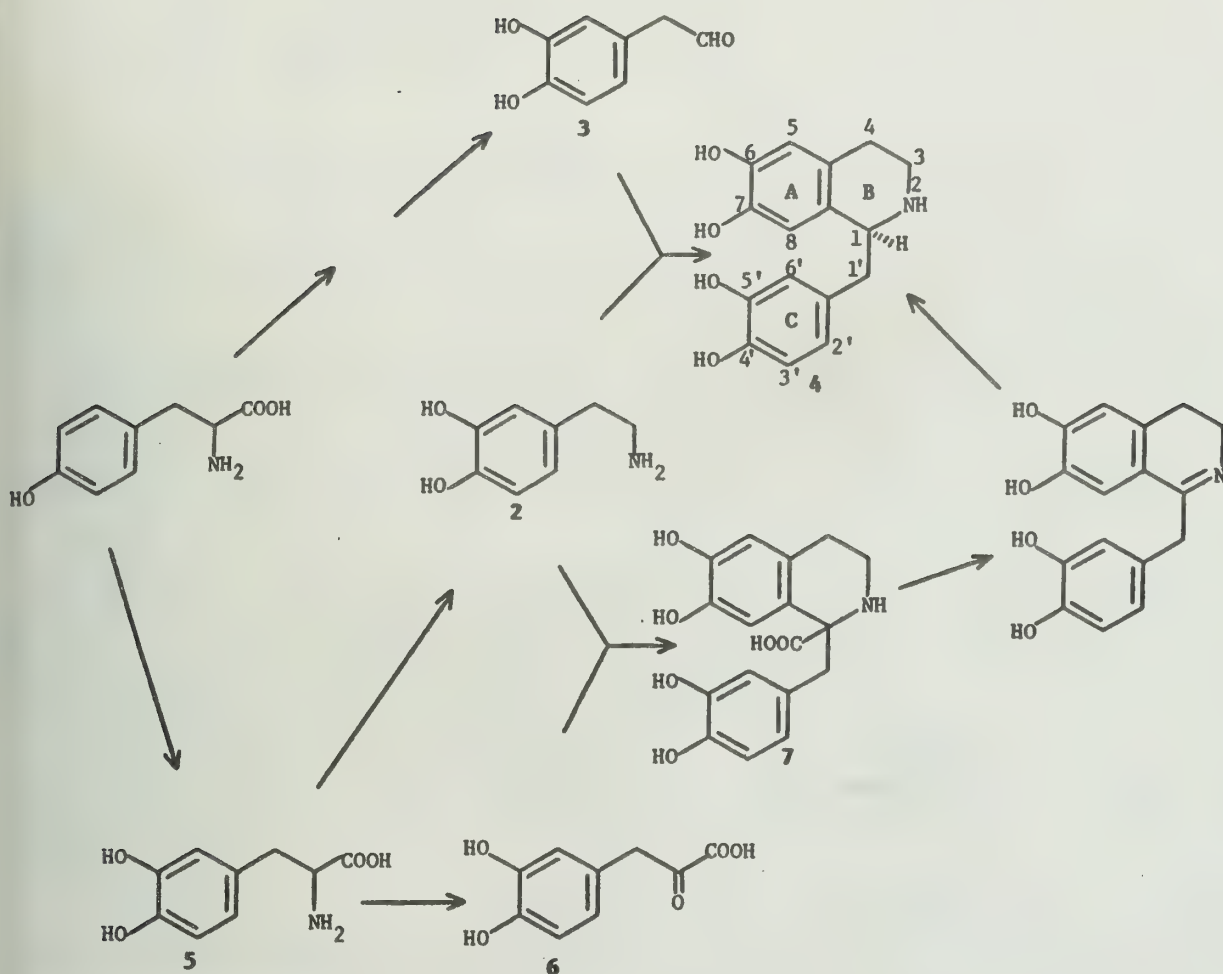
### The Biosynthesis of Norlandosoline

As early as 1910 it was envisaged that the 1-benzylisoquinoline nucleus was biosynthesized from two tyrosine molecules, one of which is converted to dopamine **2**, the other to 3,4-dihydroxyphenylacetaldehyde **3**.<sup>2</sup> A Pictet-Spengler-type condensation of these two units leads to norlaudanosoline **4**, the first isoquinoline intermediate in the pathway to a large number of benzylisoquinoline alkaloids. Tyrosine has been demonstrated to be a very efficient precursor for berberine **1** and is incorporated into both the top and bottom portion of the alkaloid, but dopamine **2** is only incorporated into the isoquinoline nucleus.<sup>3</sup> Norlaudanosoline **4** has been recognized by radioactive substrate feeding experiments as an early precursor to papaver alkaloids.<sup>4</sup> It was later postulated that DOPA **5** is converted into 3,4-dihydroxyphenylpyruvic acid **6** rather than the aldehyde **3**, and that a condensation with dopamine **2** provides norlaudanosoline-1-carboxylic acid **7**, which subsequently undergoes decarboxylation (Scheme I).<sup>5</sup>

The intermediary nature of norlaudanosoline-1-carboxylic acid **7** has been claimed to be supported by *in vivo*<sup>6</sup> and *in vitro*<sup>7</sup> experiments, but recent work with an enzyme isolated from cell suspension cultures of *Eschscholtzia tenifolia* has been shown to catalyze the stereospecific condensation of dopamine **2** with 3,4-dihydroxyphenylacetaldehyde **3** to give (*S*)-reticuline, while 3,4-dihydroxyphenylpyruvate **6** is inactive.<sup>8</sup> The reports of *in vivo* and *in*



Scheme I



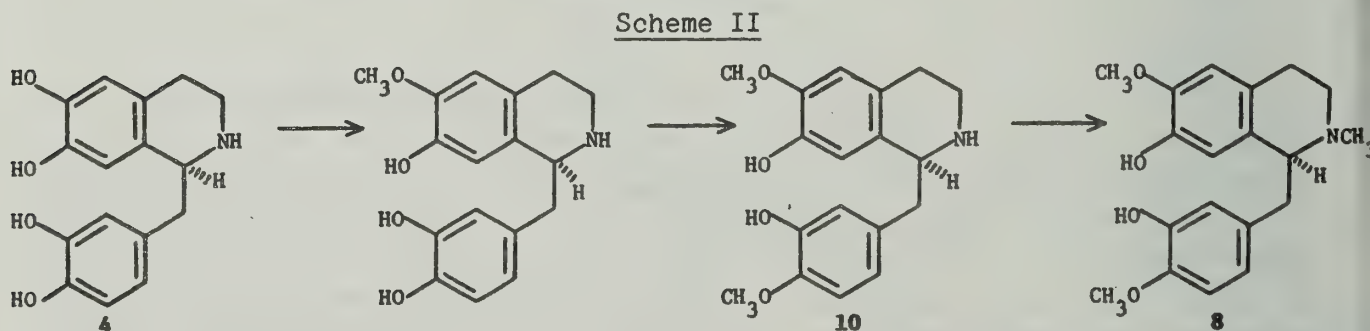
in vitro formation of norlaudanosoline-1-carboxylic acid have been explained by the ease of which phenethylamines react nonenzymatically.<sup>8</sup> The results on the incorporation of 7 have been explained by the facile air oxidative decarboxylation<sup>9</sup> or by enzymes such as peroxidases which occur widely in the plant kingdom.<sup>10</sup> The resulting 3,4-dehydroisoquinoline derivative formed could be reduced to the tetrahydroisoquinoline stage and then could be further metabolized under in vivo conditions.

## The Biosynthesis of Reticuline

Further down the pathway, reticuline 8 has proven to be an important branch point intermediate leading to protoberberines, morphinanes, proaporphines, cularines, and many other classes of benzyloquinoline alkaloids. With norlandosoline 4 firmly established as the first intermediate in benzyloquinoline biosynthesis, it must be transformed to reticuline 8 by three methylation reactions; two O-methylations at positions 6 and 4' and one N-methylation. In vitro feeding studies have demonstrated that the source of

these methyl groups is S-adenosylmethionine (SAM).<sup>11</sup> By examination of the efficiency of incorporation of differently methylated norlandosoline it was concluded that O-methylation precedes N-methylation.<sup>12</sup> An enzyme has recently been isolated from *Argemone platyceras* cell cultures that catalyzes the formation of 6-O-methylnorlaudanosoline 9, and to a small extent, 7-O-methylnorlaudanosoline from SAM and norlaudanosoline 4.<sup>13</sup> The existence of a highly specific enzyme which specifically methylates 6-O-methyl-norlaudanosoline in the 4'-position to give norreticuline 10 with SAM serving as the methyl donor is currently being purified and characterized.<sup>14</sup>

The final step in the biosynthesis of reticuline 8 is the N-methylation of norreticuline. The incorporation of norreticuline 10 into 8 has been demonstrated in vivo,<sup>15</sup> and an enzyme has been isolated and purified which catalyzes the same conversion in the presence of SAM.<sup>16</sup> The enzyme has been found in both the differentiated plants and cell cultures of several protoberberine-containing plant families. The biosynthesis of reticuline 8 from norlaudanosoline 4 is summarized in Scheme II.



### The Biosynthesis of Berberine

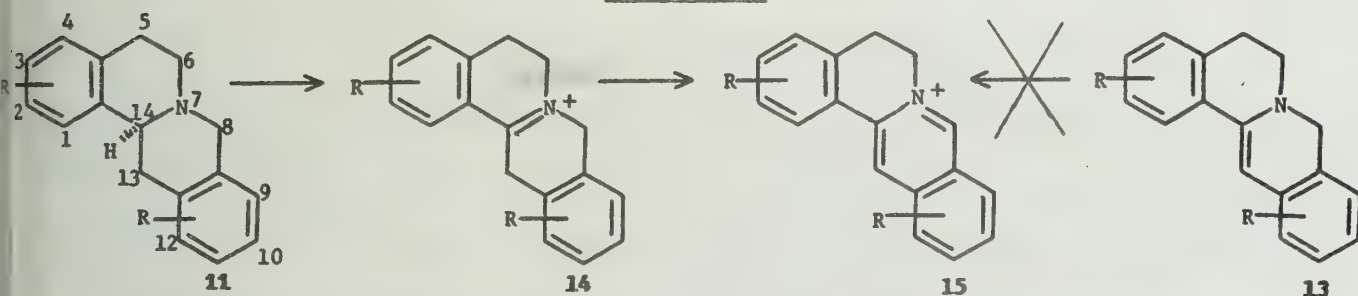
A number of early studies show that the N-methyl group of reticuline 8 is converted into the "berberine bridge" in berberine 1.<sup>17</sup> Recent work has shown that a single enzyme catalyzes the cyclization of 8 to (S)-scoulerine 11, while the (R)-form of 8 was totally inactive.<sup>18</sup> The enzyme also showed no activity towards either (R)- or (S)-reticuline-N-oxide, which were previously suggested as possible intermediates.<sup>19</sup> The enzyme does not require a co-factor and acts only on reticuline 8 and laudanidine. An essential prerequisite for the enzymatic conversion is the presence of an unsubstituted hydroxy group at the C-5' position of the tetrahydrobenzylisoquinoline system.

The initial cyclization of 8 is followed by several steps involving methylation, oxidation, and another cyclization to yield berberine 1. Evidence that the next step in the biosynthesis is methylation at the 9-position has recently been provided by work with crude cell-free homogenates of *Berberis*

cell cultures.<sup>20</sup> Incubation of labeled scoulerine **11** with the homogenate in the presence of SAM produced tetrahydrocolumbamine **12**. The enzyme acts preferentially on scoulerine **11** and not the oxidized scoulerine derivative with an aromatic C-ring, and shows high specificity for the 9-hydroxy position of **11**.

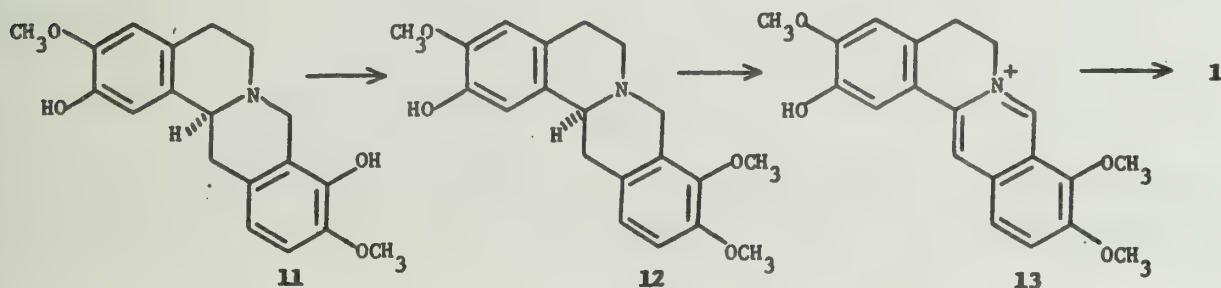
The next step in the formation of the protoberberine skeleton is the oxidation of the C-ring of the tetrahydroprotoberberines. A flavin enzyme that catalyzes the dehydrogenation of more than 20 different tetrahydroprotoberberines to the corresponding protoberberine alkaloids in the presence of oxygen has been isolated and purified.<sup>21</sup> Since 13,14-dehydroprotoberberines **13** were not oxidized it was concluded that the enzyme catalyzes the dehydrogenation of the tetrahydroprotoberberine molecule at C-14 and N-7 and that the 7,14-dehydroberbinium **14** intermediate aromatizes further in ring C to afford the protoberberine skeleton **15** (Scheme III).

Scheme III



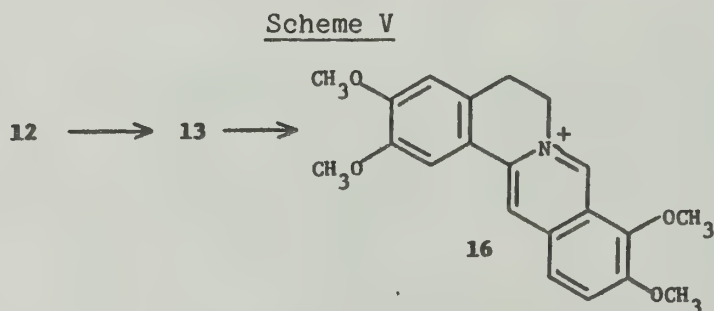
Oxidation of tetrahydrocolumbamine **12** yields columbamine **13**, the immediate precursor of berberine. The final step in the pathway involves the formation of the methylenedioxy group, which has been shown to be formed from an *o*-methoxy phenol precursor.<sup>22</sup> A purified  $\text{Fe}^{2+}$ -containing enzyme isolated from *Berberis* cell cultures catalyzes the formation of the methylenedioxy group in berberine **1** from columbamine **13**.<sup>23</sup> The enzyme is specific for **13**; tetrahydrocolumbamine **12** did not act as a substrate as had previously been assumed.<sup>24</sup> The currently accepted biosynthetic pathway to berberine from reticuline is shown in Scheme IV.

Scheme IV

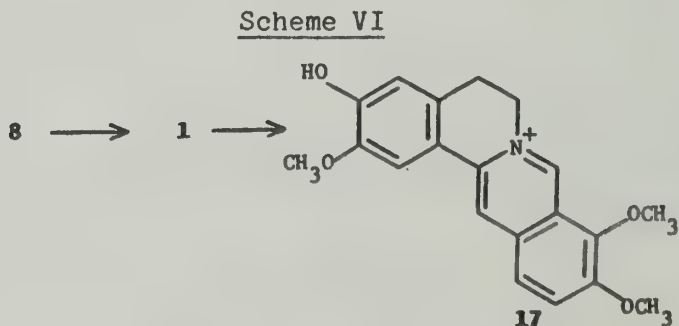


### The Biosynthesis of Other Protoberberine Alkaloids

The biosynthesis of palmatine **16** from tetrahydrocolumbamine **12** requires a methylation and an oxidation. Although there has been some controversy over the actual sequence, an enzyme which converts columbamine **13** to palmatine **16** in the presence of SAM has been isolated.<sup>25</sup> The enzyme shows no activity with the tetrahydrocolumbamine **12**, which suggests that oxidation precedes methylation (Scheme V).



Jatrorrhizine **17** is the major alkaloid of *Berberis* cell cultures.<sup>26</sup> It contains an unusual 2-O-methyl group, which makes it difficult to deduce its biosynthetic origin from reticuline **8**. The methylation pattern requires one of three possibilities: (i) **8** is not the only entry point to the protoberberines; (ii) palmatine **16** is demethylated; or (iii) transfer of a methyl group from one oxygen to another by way of a methylenedioxy group. Results of experiments with *Berberis* suspension cell cultures have shown that reticuline **8** and berberine **1** are both incorporated into jatrorrhizine **17**, indicating that the methyl group of **8** is transferred to the 2-position through **1** (Scheme VI).<sup>27</sup>



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# DIASTEREOSELECTIVITY IN ORGANOMETALLIC ADDITIONS TO C=N DOUBLE BOND

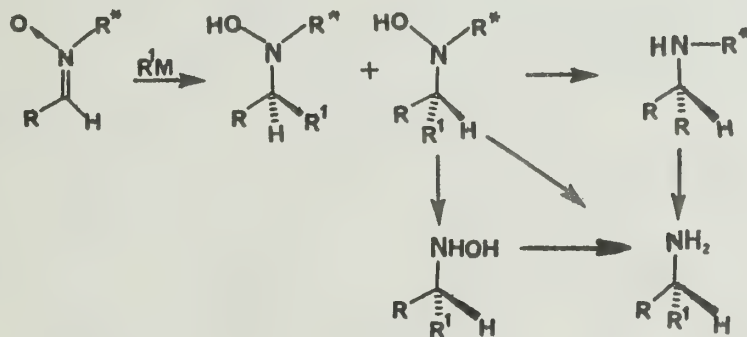
Reported by Zen-Yu Chang

May 5, 1986

Organometallic addition to imines is one of the many methods which has been used to synthesize amines. However, this approach is generally limited to N-substituted imines lacking an  $\alpha$ -hydrogen and is rather restricted owing to the poor reactivity and instability of these compounds.

Since it is well appreciated that the relative and absolute configuration of any chiral centers present in biologically active compounds are important factors in determining receptor affinity and biological activities, stereospecific synthesis of chiral amines is desired. Although chiral amines could be obtained by stereospecific reduction of imines,<sup>1</sup> the complementary reactions of imines with carbon nucleophiles, including Grignard reagents,<sup>1,2</sup> organolithiums,<sup>2a,c,f,3</sup> organoboranes,<sup>2h,i,3,4</sup> organostannanes,<sup>2f</sup> cyanide ion,<sup>5</sup> organozinc,<sup>2h,i</sup> organotitanium,<sup>2h,i,3b</sup> and organoaluminum,<sup>2i,3b</sup> have been reported.

In contrast to imines, nitrones are more stable and undergo smooth addition reactions with various carbon nucleophiles such as Grignard reagents,<sup>6</sup> organolithium,<sup>7</sup> cyanide ion,<sup>6</sup> and Reformatsky reagents.<sup>8</sup> The polarized imine double bond of the nitron is responsible for their high reactivity towards nucleophiles. If high diastereoselectivity is realized with nitrones,<sup>9</sup> such addition reaction may be practical and useful for the synthesis of chiral amines, hydroxylamines, amino alcohols and other polyfunctional nitrogenous compounds. For amine synthesis, it is necessary to develop useful procedures for deoxygenation and dealkylation of the resulting hydroxylamine adducts. The diastereoselectivity in the reaction of organolithium and Grignard reagents with certain nitrones will be discussed.



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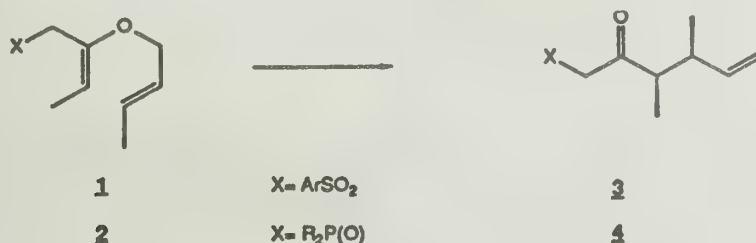


# PHOSPHORUS-STABILIZED, CARBANION-ACCELERATED CLAISEN REARRANGEMENTS

Reported by John Marlin

May 8, 1986

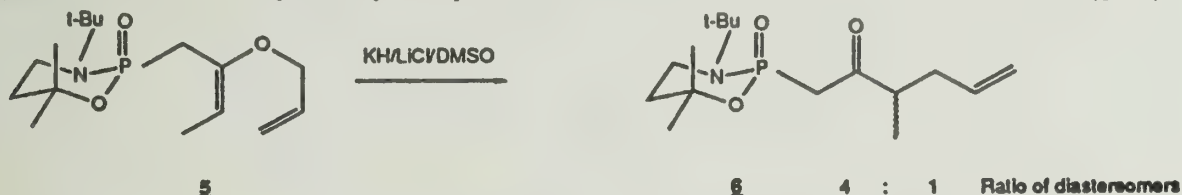
The Claisen rearrangement has enjoyed tremendous success as a synthetic tool for natural product chemists.<sup>1</sup> Furthermore, a large number of variants now exist which allow direct routes to ketones,<sup>2</sup> amides,<sup>3</sup> esters,<sup>4</sup> acids,<sup>5</sup> lactones,<sup>6</sup> and thioesters.<sup>7</sup> A trend exists among the variants that have donor substituents at C(2) of the allyl vinyl ether: the more powerful the electron donating substituent, the more facile the [3,3] sigmatropic transformation becomes.<sup>8</sup> Indeed, sulfone-stabilized, carbanion-accelerated Claisen rearrangements (1→3) only require temperatures of 25-50°C.<sup>9</sup>



The extension of the carbanion-accelerated Claisen rearrangement to include phosphorus carbanion-stabilizing groups (2→4) offers many advantages over sulfur. First, phosphorus-stabilized carbanions have higher pKa values than the corresponding sulfones and should thus be better  $\pi$ -donors.<sup>10</sup> Second, there is a broad range of ligands that bond to phosphorus making it easy to "tailor" the pKa of the stabilized anion. Third, phosphorus has the potential for chirality which makes it possible to study absolute asymmetric induction via chiral recoverable auxiliaries. Finally, the possibility exists for stereospecific phosphorus-carbon bond cleavage.

Phosphorus-stabilized, carbanion-accelerated Claisen rearrangements are efficient with diphenyl phosphine oxides and di-*t*-butyl phosphonates. The reactions are fast, clean, and produce good yields of  $\beta$ -ketophosphono derivatives with high regio- and stereoselectivity.

Preliminary results with chiral oxazaphosphorinanes indicate that phosphorus induced asymmetry is possible with this carbanionic variant (5→6).



Future work is aimed at modification of the phosphorus auxiliary, substituents on the allyl vinyl ether, and reaction conditions in order to maximize the diastereoselectivity.

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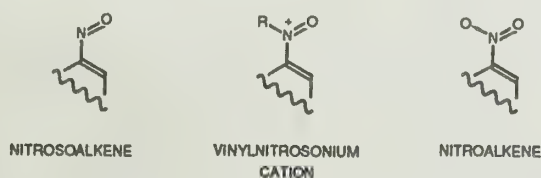
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# HETERODIENE [4+2] CYCLOADDITIONS: AN AFTERNOON WITH N,O-BONDS

Reported by Christopher J. Cramer

May 12, 1986

Recent work directed towards the total synthesis of heterocyclic natural products has involved modification of the classical Diels-Alder reaction<sup>1</sup> by incorporation of heteroatoms into the diene and/or dienophile which participate in the [4+2] cycloaddition.<sup>2</sup> These heterocycloadditions often exhibit the same level of regio- and stereochemical control at four contiguous centers as their all carbon analogues. Although a stereocenter may be sacrificed due to the astereogenicity<sup>3</sup> of a given heteroatom (e.g. oxygen or sulfur), this is compensated by the potential for elaboration of the latent functionality incorporated into the heterocyclic product.



Three N,O Heterodienes  
Figure 1

The inter- and intramolecular cycloadditions of three related heterodienes, nitrosoalkenes,<sup>4,5d</sup> vinylnitrosonium cations,<sup>5</sup> and nitroalkenes<sup>6</sup> (Figure 1) have all been studied. The first two cases suffer from under- and overreactivity respectively in intermolecular examples,<sup>4a-c,5a-c</sup> but these limitations may largely be overcome by intramolecularization.<sup>4d,e,5d</sup> With nitroalkenes the use of nucleophilic dienophiles was formerly required, and products arose not through formal [4+2] cycloadditions, but through 1,4 dipolar cycloadditions.<sup>2a,6a-d</sup> The use of a Lewis acid catalyst, however, has recently revealed a potential for reaction with unactivated olefins as dienophiles, in a process where bond formation at the ends of the two reactive termini is completely stereochemically coupled.<sup>6e</sup>

Methods for the subsequent elaboration of the 5,6-dihydro-4H- and tetrahydro[1,2]oxazines formed from the first two heterodienes respectively have remained surprisingly elusive. However, the cyclic nitronic esters formed from nitroalkenes have proved readily convertible into a wide variety of functionalized products.

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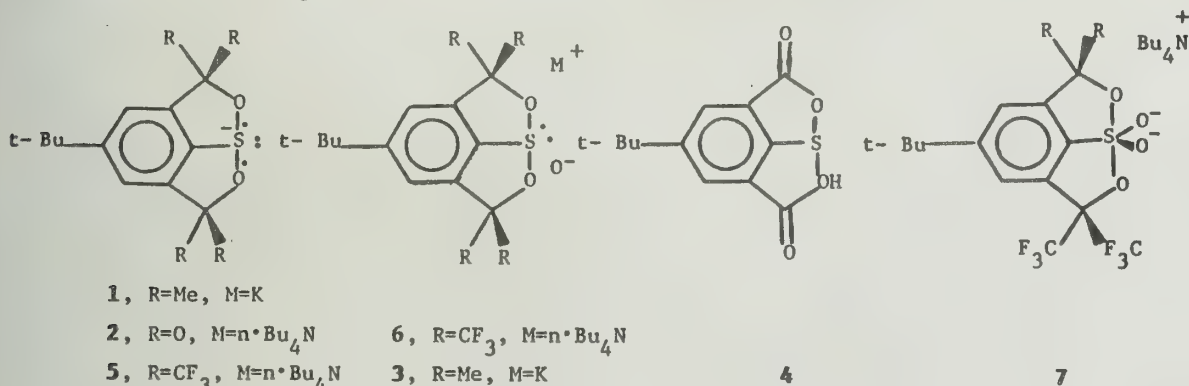
# UNUSUAL REACTIVITY OF SOME HYPERVALENT ORGANIC SULFUR COMPOUNDS

Reported by Joseph C. Rongione

Vanderbilt University  
Nashville, TN

Hypervalent sulfur compounds have been proposed as intermediates or as high energy transition states in the reactions of sulfoxides, sulfonium ions and sulfides.<sup>1-3</sup> The first hypervalent sulfur compound synthesized was  $\text{SCl}_4$ , a highly reactive species.<sup>4</sup> Since then stable organic hypervalent sulfur compounds have been prepared,<sup>5</sup> facilitating the study of these compounds.

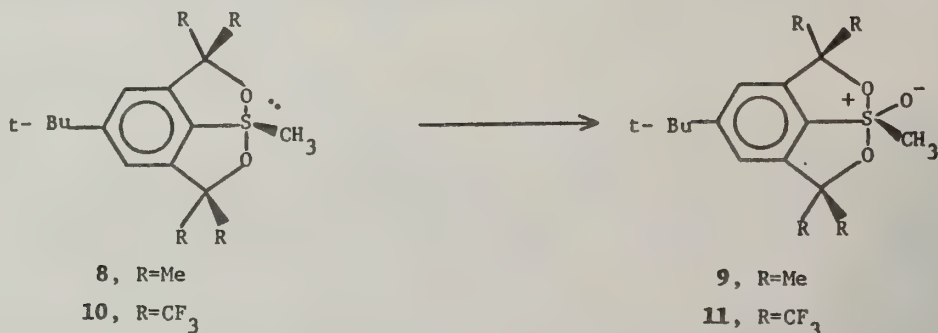
Hypervalent refers to compounds with a main group central atom which possess at least one 3-center 4-electron bond.<sup>6</sup>



Lau prepared stable examples of a a sulfuranide (1,2) and a sulfuranide oxide (3).<sup>5</sup> These compounds were symmetrical as evidenced by NMR data at low temperature. Sulfuranide 2 showed only one carbonyl stretching frequency in the IR. This stretching frequency ( $1639\text{ cm}^{-1}$ ) is of lower frequency than of the two stretching frequencies of the unsymmetrical starting material 4 ( $1736\text{ cm}^{-1}$  carbonyl of the carboxylic-sulfinic acid anhydride) and  $1670\text{ cm}^{-1}$  (carboxyl carbonyl)). The single carbonyl stretching frequency of 2 is strongly supportive of a closed species with some electron density delocalized onto the apical ligands. One would expect this, given the molecular orbital diagram suggested by Rundle<sup>8</sup> and Pimentel<sup>9</sup> and discussed at length by Musher.<sup>10</sup> The HOMO has its electron density centered on the apical ligands. Attack of electrophiles on compounds 1-3 occurs predominantly at the apical positions.

Perkins synthesized the gem-bis(trifluoromethyl) derivatives of 1 (5) and 3 (6) and also prepared 7.<sup>11</sup> These compounds (5-7) were also determined to be symmetrical by NMR at low temperature and by their x-ray structures. Estimations of the  $\text{pK}_a$ 's of the acids of 5-7 (which are open) using the Hammett equations gave values of 9.9, 9.3, and 9.1  $\text{pK}_a$  units for 5, 6 and 7 respectively.<sup>11</sup> Actual titrimetric  $\text{pK}_a$ 's were found to be 4.4, 5.0 and 7.2  $\text{pK}_a$  units for 5, 6 and 7 respectively. An explanation for the estimated energy difference between the open and closed (most stable form) forms of the anions

is that the Hammett equations does not take into account through space interactions.<sup>11</sup>



Methyl iodide reacted with **1** at an equatorial site, forming sulfurane **8** in excellent yield (92%).<sup>12</sup> The methyl protons to the sulfur in **8** underwent complete deuteration in pyridine- $d_5$  with added 20% NaOD- $D_2O$  in eight days. Oxidation of **8** to sulfurane oxide **9** via  $KMnO_4$  resulted in more acidic methyl protons to the sulfur. Complete deuterium exchange of the methyl protons in **9** showed negligible exchange under the same conditions.<sup>12</sup>

Syntheses of sulfurane **10** and sulfurane oxide **1** were accomplished using a route very closely related to the one used by Perkins.<sup>11</sup> The rates of S-methyl deuteration of sulfurane oxides **9** and **11** in  $CD_3OD$  at low temperature was studied. The kinetic acidity of **9** was found to be orders of magnitude greater than the kinetic acidity of **11**. Mechanistic studies of this unusual reversal of kinetic acidities have been undertaken. The reactions of sulfurane **10** and sulfurane oxide **11** and a possible explanation for the unexpected order of rates of deuteration of **9** and **11** will be discussed in this seminar.

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**ORGANIC SEMINAR ABSTRACTS**

**1986-87, SEMESTER I**

**University of Illinois**

**School of Chemical Sciences**

**Department of Chemistry**

**University of Illinois**

**Urbana, Illinois 61801**

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# A CRITICAL EVALUATION OF BALDWIN'S RULES FOR RING CLOSURE

Reported by Nelson T. Rotto

August 28, 1986

Professor Jack E. Baldwin introduced a set of rules in 1976 to predict the relative facility of ring forming reactions.<sup>1</sup> These rules are empirically based and were primarily aimed to aid synthetic organic chemists. The rules are as follows:

- 1) Tetrahedral systems: 3- to 7-exo-tet are all favored; 5- and 6-endo-tet are disfavored.
- 2) Trigonal systems: 3- to 7-exo-trig are all favored; 3-to 5-endo-trig are disfavored; 6- and 7-endo-trig are favored.
- 3) Digonal systems: 3- and 4-exo-dig are disfavored; 5- to 7-exo-dig are favored, and 3- to 7-endo-dig are all favored.

Since publication of the rules, Baldwin has presented other papers either giving experimental evidence for his rules<sup>2</sup> or extending the rules to intramolecular enolate reactions.<sup>3</sup> The purpose of this report is to evaluate Baldwin's rules for ring closure based on more recent theoretical findings and experimental observations. This report does not include radical cyclizations or ring closures onto three-member rings.

## I. Closures onto Double Bonds.

Baldwin's ring closure rules at trigonal centers are primarily based on trajectory angle  $\alpha$  (Fig. 1) found to be between  $100^\circ$  and  $110^\circ$  for nucleophilic attack on carbonyl groups.<sup>4</sup>

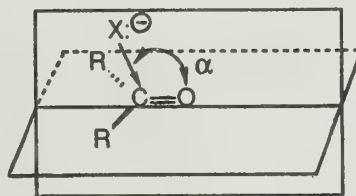


Figure 1

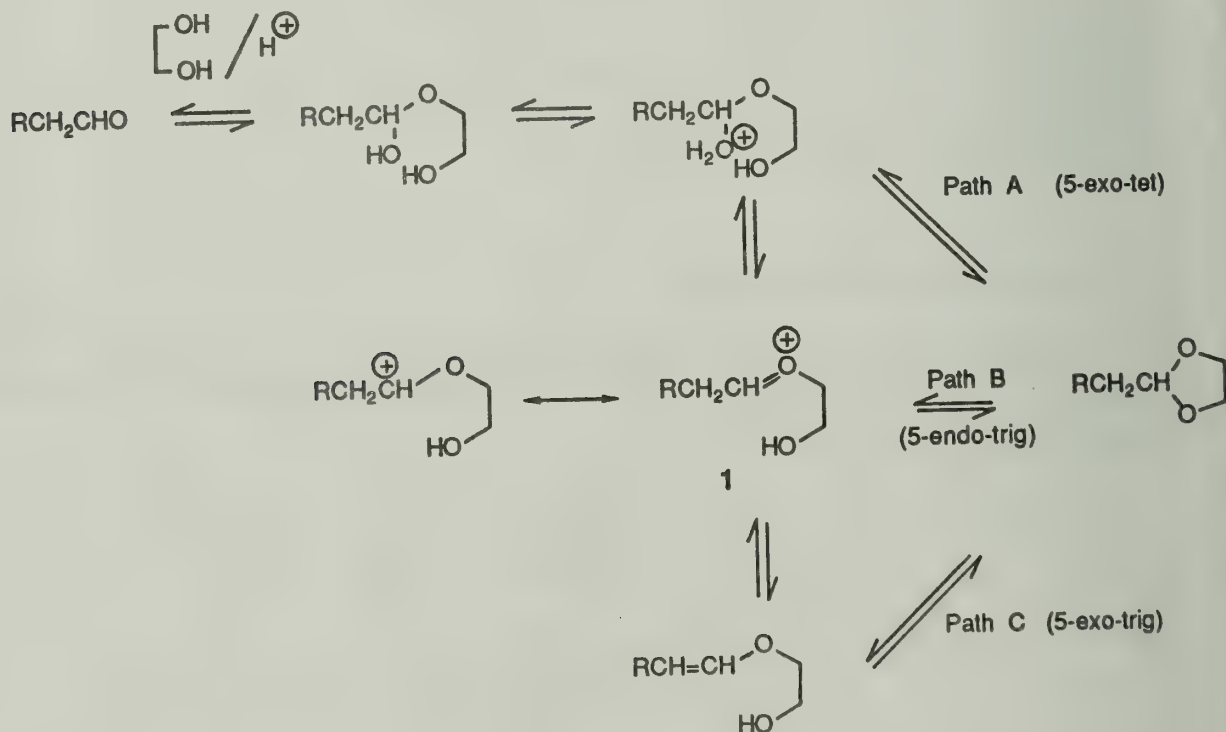
More recently, similar calculations on carbonyl groups and olefins have produced very similar results.<sup>5</sup>

Also vital to Baldwin's rules is the extent of deviation allowed in the nucleophile's trajectory. Houk<sup>23</sup> has calculated the energy cost of varying the trajectory of hydride onto propene. A change of in-plane ( $C-C-H$ ) angle by  $10^\circ$  or out-of-plane angle by  $11^\circ$  increases the calculated transition state energy by 1.36 kcal/mole causing a tenfold decrease in reaction rate (Houk, however, claims these calculations may overestimate the flexibility of the transition state).

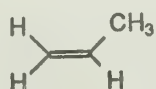
Menger<sup>6</sup> has proposed that transition states are "floppy" and do not lie on a saddle point beneath steep walls but rather in a shallow "glaciated" valley where geometric flexibility and mobility are possible. Menger claims that nucleophiles attack through a relatively broad "reaction window" and are not constrained to a narrow attack trajectory; evidence has been cited<sup>6</sup> to support this claim.

The most controversial of Baldwin's rules is the 5-endo-trig closure which has been labelled "disfavored". Baldwin claims that a substantial kinetic barrier arising from unfavorable orbital overlap prevents this ring closure form competing effectively with alternative reaction pathways. A classic example illustrating the 5-endo-trig closure is the mechanism of cyclic acetal formation<sup>7</sup> (Scheme I).

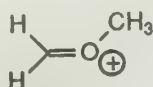
Scheme I



Three pathways are conceivable, but path C can be eliminated as the exclusive mechanism since benzaldehyde readily forms a cyclic acetal. Furthermore, Baldwin reports no deuterium exchange  $\alpha$  to the carbonyl during ketalization of acetone.<sup>1c</sup> Path B involves a "disfavored" 5-endo-trig closure onto an alkylideneoxonium ion (1). Calculations,<sup>8</sup> however, have shown the twisting barrier of 2 to be 60.33 Kcal/mole while 3 is only 18.77 Kcal/mole (molecules twisted 90°). Because of this flexibility, alkylideneoxonium ions should not be grouped with carbon-carbon double bonds and treated accordingly; hence path B (Scheme I) is not necessarily "disfavored" and should not be eliminated from consideration based solely on Baldwin's rules.

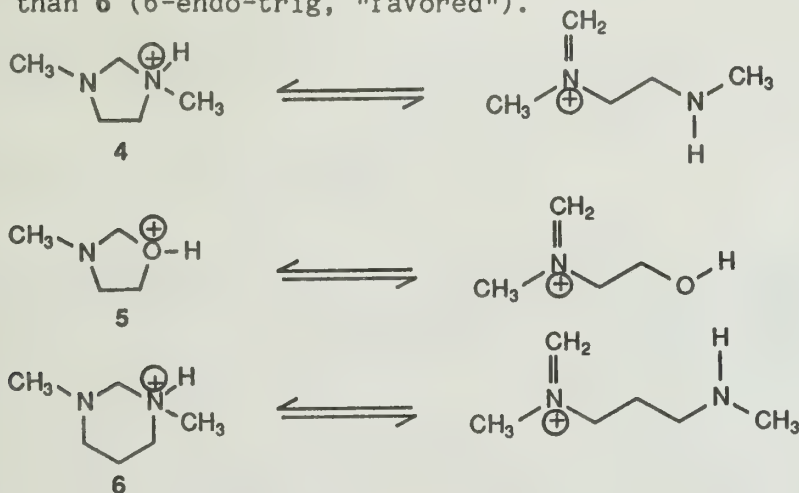


2

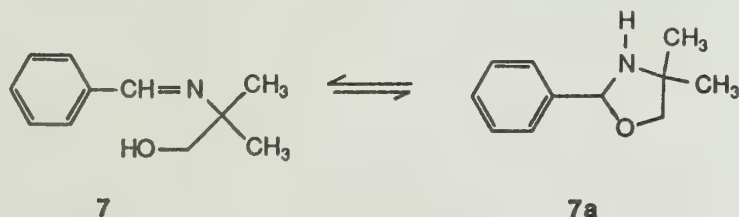


3

Ring-chain tautomerization of 1,3-dimethyl-1,3-diazolidine (4) and 1-methyl-1,3-oxazolidene (5) in acidic media has been shown to be a relatively rapid 5-endo-trig reaction.<sup>9</sup> Monitoring the equilibria by <sup>1</sup>H NMR shows the open-chain tautomers to be 10-20% of the mixture at room temperature. Interestingly, the rate of ring opening of 4 (5-endo-trig, "disfavored") was found to be faster than 6 (6-endo-trig, "favored").



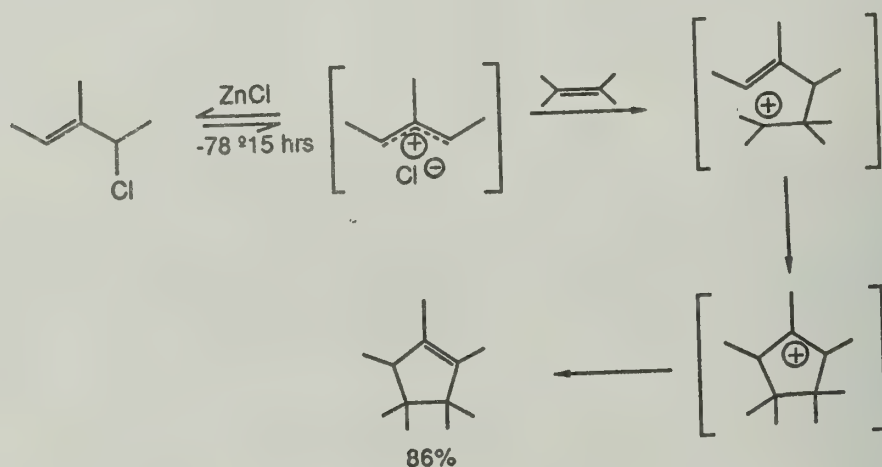
Further ring-chain tautomerization studies<sup>10</sup> on oxazolidines showed that 7 is in rapid equilibrium with 7a in neutral media; <sup>1</sup>H NMR measurements on 7 in various solvents show that equilibrium is attained within 18 seconds.



Other examples of relatively facile 5-endo-trig cyclizations onto imine bonds can be found in the literature.<sup>11</sup> Imine and iminium double bonds appear to have relatively large "reaction windows" and facile 5-endo-trig closures are not hindered by any substantial "kinetic barrier".

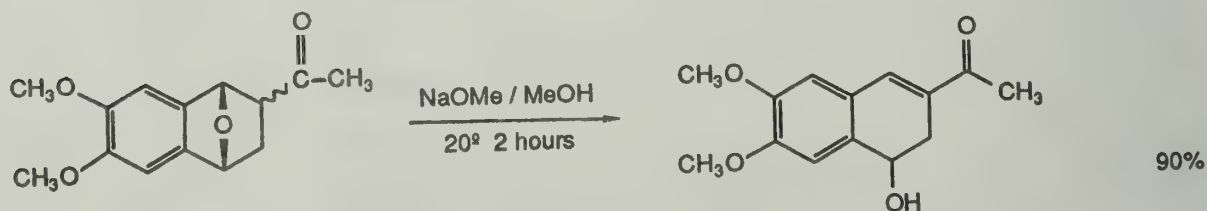
There is a substantial number of 5-endo-trig reactions on carbon-carbon double bonds which have been reported in the literature, and some of these reactions occur under very mild conditions. The cyclization reaction in Scheme II was reported,<sup>12</sup> and only the 5-endo-trig product was isolated.

Scheme II



A very facile retro-5-endo-trig ring opening has been reported in a 7-oxabicyclo[2.2.1]heptane system<sup>13</sup> (Scheme III).

Scheme III

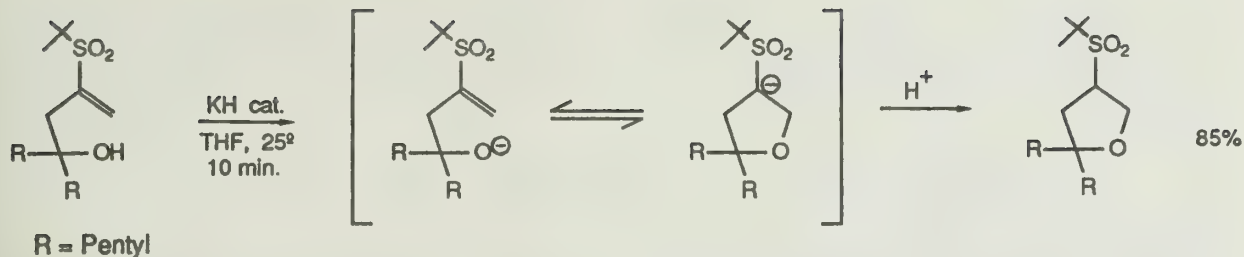


The authors claim that the unique geometry of the furan ring in the bicyclic system allows the necessary orbital overlap for the reaction to take place.

Unsaturated sulfones cyclize readily in a 5-endo-trig process under very mild conditions<sup>14</sup> (Scheme IV).

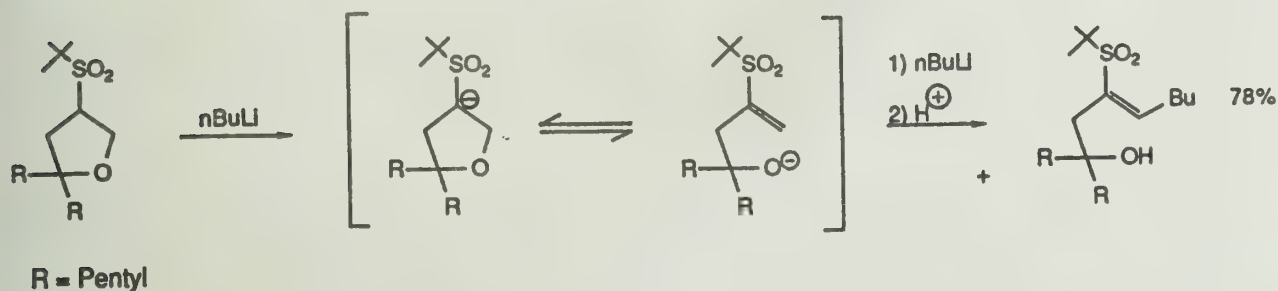


Scheme IV



The authors claim an equilibrium exists between cyclic and acyclic anions by the following experiment (Scheme V).

Scheme V



It should be noted that the corresponding sulfoxide did not cyclize. Many other examples of 5-endo-trig closures onto carbon-carbon double bonds exist in the literature.<sup>15</sup>

## II. Closures onto Triple Bonds.

Baldwin claims that all endo-dig closures are favored whereas only 5,6, and 7-exo-dig closures are favored.<sup>1a</sup> This preference for endo closure at digonal centers is one of the more controversial aspects of Baldwin's rules. Others<sup>16</sup> have reported a predominance of exo cyclization at digonal centers in the formation of 5-7 member rings, and this general predominance of exo-dig closure has also been documented by this reporter through a survey of the literature since 1977. Through actual experimentation, the preference of 5-exo-dig closure over 6-endo-dig closure has been reported.<sup>17</sup>

The digonal closure rules are also based on the suggestion by Baldwin that the approach of a nucleophile onto a triple bond occurs via the acute angle<sup>1a</sup> ( $\alpha = 60^\circ$ ) shown below (Fig. 2).

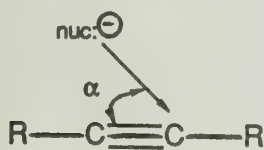


Figure 2

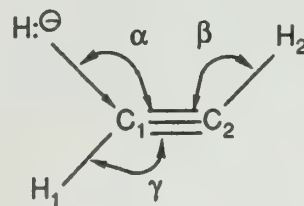


Figure 3

Baldwin makes this suggestion based on reported photochemical polymerizations of diacetylenes.<sup>1a</sup> Dykstra,<sup>18</sup> however, has studied the nucleophilic attack of hydride on acetylene using ab initio molecular wave functions and has found the preferred attack trajectory (angle  $\alpha$ , Fig. 3) to be  $127.8^\circ$  with the hydride 2.097 Å from  $C_1$ . The acetylenic hydrogens ( $H_1$  and  $H_2$ ) were distorted into a trans position with angles  $\gamma$  and  $\beta$  corresponding to  $146.8^\circ$  and  $128.0^\circ$  respectively.

Many other investigations on the nucleophilic attack on triple bonds have reported similar results.<sup>19</sup> Baldwin's proposed acute angle of attack (Fig. 2) clearly has no theoretical support. Calculations unanimously indicate that nucleophiles attack triple bonds via obtuse angles which is very similar to nucleophilic attack on double bonds. The trans distortion of the acetylenic fragment in the transition state (Fig. 4) permits the optimal geometry for 5-endo-dig closures<sup>20</sup> (Fig. 3), and indeed, cases of 5-endo-dig closures are reported in the literature.<sup>22</sup> Examples of 6-endo and 7-endo-dig closures are reported by Baldwin.<sup>1a</sup>

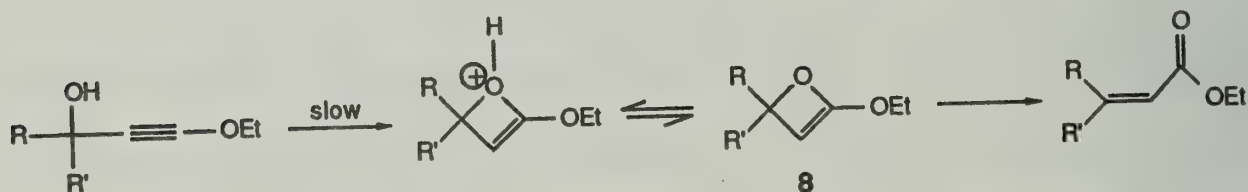
For 3-endo or 4-endo-dig closures, however, such distortion appears to be insufficient to orient the nucleophile to the "reaction window"; yet both of these ring closures are predicted to be "favored" by Baldwin.<sup>1a</sup> Baldwin does not cite any examples of 3-endo-dig closures, and none have been reported in



Figure 4

the literature since publication of Baldwin's rules in 1976. Baldwin cites the proposed mechanism (Scheme VI) for ethoxyethynyl carbinol- $\alpha,\beta$  unsaturated ester rearrangement as precedent for 4-endo-dig closures.

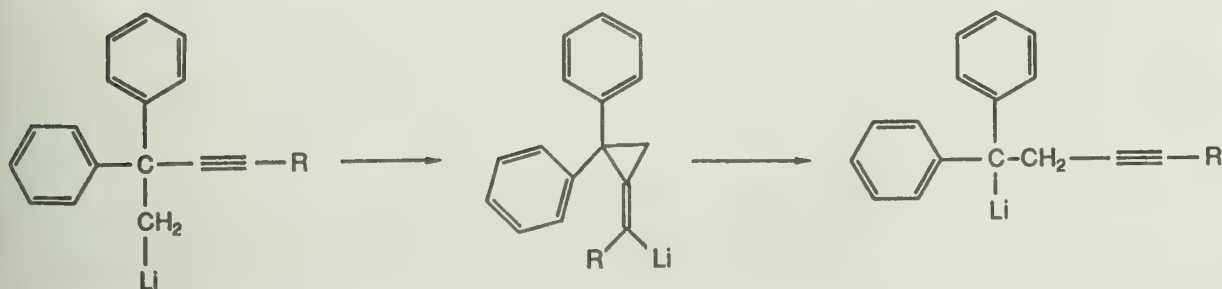
Scheme VI



However, the proposed oxetane intermediate **8** (Scheme VII) has not been isolated or detected. No examples of 4-endo-dig ring closures have been reported since 1976.

The accepted theory of obtuse attack angle on acetylenes (Fig. 3) suggests the possibility of 3-exo-dig and 4-exo-dig closures (disfavored by Baldwin's rules). The [1,2]sigmatropic shift of an acetylene group through a 3-exo-dig closure has been proposed<sup>21</sup> (Scheme VIII).

Scheme VIII



No examples of 4-exo-dig ring closures are reported in the literature.

## Conclusion

Baldwin's rules for ring closure at digonal centers are clearly based on ideas of nucleophilic attack onto triple bonds which are inconsistent with current theoretical findings; these rules should be reconsidered. Ring closures at trigonal centers, especially alkylideneoxonium ions, iminium ions and imines, are not necessarily disfavored in 5-endo cases since these double bonds have structural properties and reactivity different from carbon-carbon double bonds. The 5-endo-trig ring closure onto carbon-carbon double bonds are borderline cases since a number of examples show little if any kinetic barrier to cyclization. Despite these criticisms, Baldwin's rules have succeeded in focusing attention on the importance of stereoelectronics and nucleophile trajectories in cyclization reactions.

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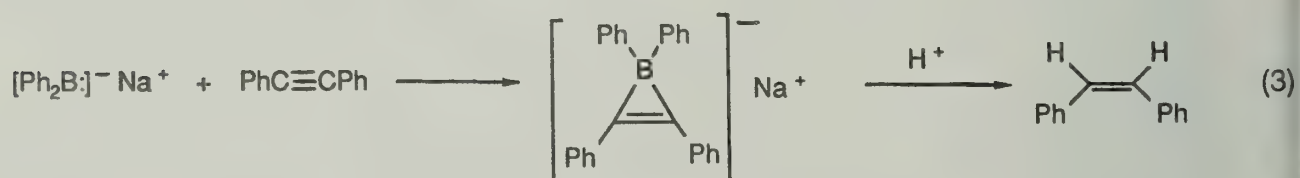
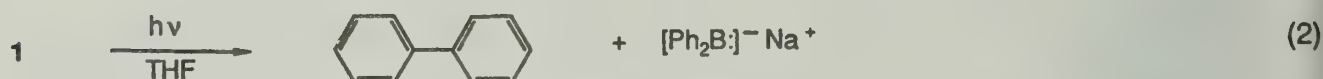
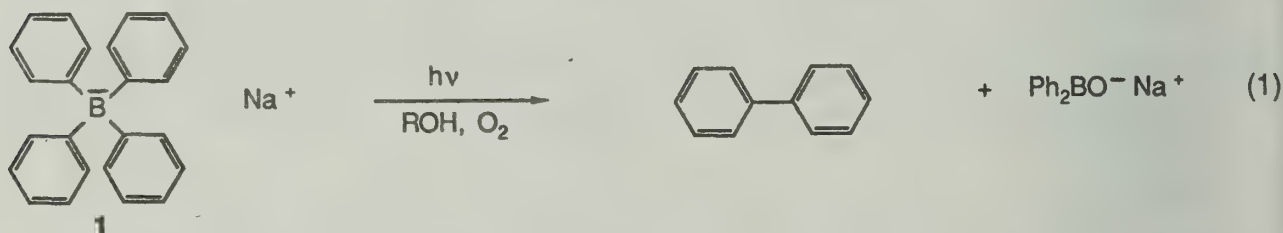
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**PHOTOCHEMICAL AND ELECTRON-TRANSFER SENSITIZED REARRANGEMENTS  
OF TETRAARYLBORATE SALTS**

Reported by John Wilkey

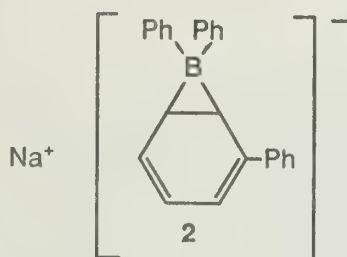
September 15, 1986

The photochemical rearrangement of tetraarylborate salts has been the subject of numerous investigations under a range of experimental conditions.<sup>1</sup> However, differing mechanisms have been proposed to account for the observed products. The direct irradiation of sodium tetraphenylborate (**1**) in protic solvents has been reported by Williams and coworkers.<sup>2</sup> In solutions containing dissolved oxygen, biphenyl is the major product. In nitrogen-purged solutions, dihydrobiphenyls predominate. Labeling experiments reveal the coupling of aryl groups occurs intramolecularly and that the new bond in the biaryl product is formed from carbon atoms formerly bound to boron. Further results led to the postulation of a mechanism involving bridging boron intermediates.<sup>3</sup>



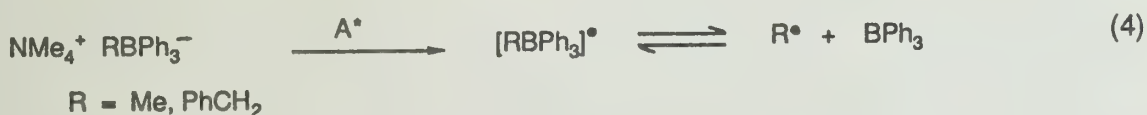
The direct irradiation of **1** in ether solvents is purported to result in the direct formation of biphenyl and diphenylborene.<sup>4</sup> Photolysis of **1** in solutions containing diphenylacetylene as a presumed trap for the borene produced stilbenes upon acidic workup. The formation of the latter was taken as evidence for the existence of diphenylborene. However, experiments performed in these laboratories reveal that the stilbenes arise by an electron transfer mechanism.<sup>5</sup> Furthermore, our reexamination of the photolysis of **1** in THF and acetonitrile reveals that biphenyl is not a primary photochemical product, but arises from ground- or excited-state reactions of the first-formed 7-borabicyclo[4.1.0]hepta-2,4-diene intermediate (**2**). This intermediate has been characterized by chemical and spectroscopic means; however, its isolation has not been accomplished owing to its extreme sensitivity toward oxygen and

water. Reaction of 2 with oxygen results in the formation of biphenyl and the sodium salt of diphenylborinic acid. Treatment of 2 with acetic acid produces 1-phenyl-1,4-cyclohexadiene. No evidence for the formation of diphenylborene was observed.



The low oxidation potential of 1 makes it a suitable donor for electron transfer reactions. Electrochemical oxidation of 1 has been reported to produce biphenyl in a two-electron process, without the intermediacy of free phenyl radicals.<sup>6</sup> Fluorescence quenching and laser spectroscopic studies reveal that 1 may be oxidized by excited state electron acceptors, such as 1,4-dicyanonaphthalene (DCN).<sup>5</sup> The biphenyl produced in this reaction has been shown to arise intramolecularly, with the same position of coupling as in the direct irradiation. Diphenylacetylene is also capable of oxidizing 1. In THF stilbenes are produced. Therefore, the previous claim for the existence of diphenylborene based upon the production of stilbenes is without justification.

In contrast to 1, the reaction of DCN with alkyltriphenylborates does produce free radicals in solution.<sup>7</sup> Radical coupling produces the alkylated acceptor. This alkylation reaction has been extended to other electron acceptors.<sup>8</sup>



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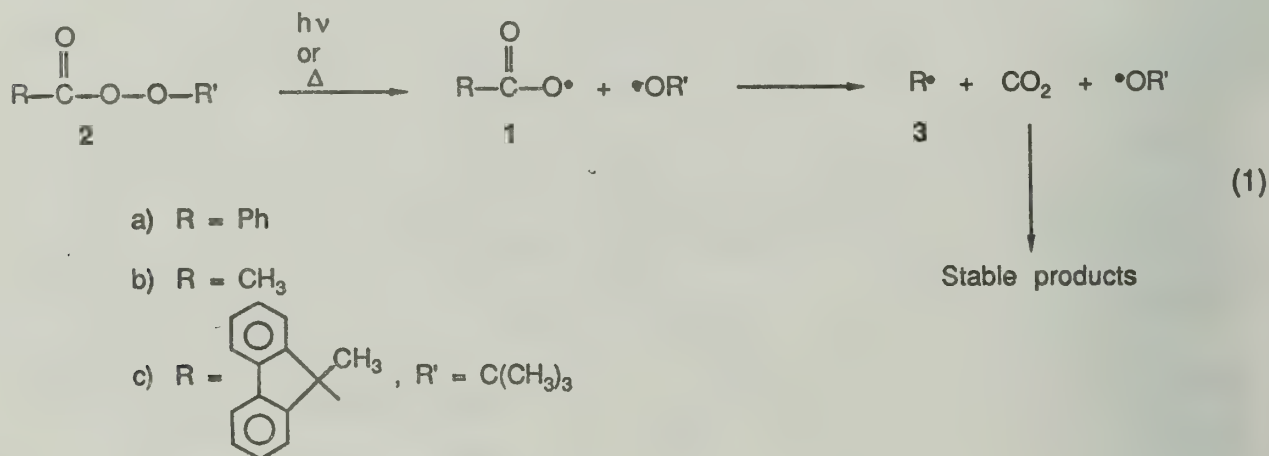
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# THE PICOSECOND PHOTOCHEMISTRY OF PERESTERS: EVIDENCE FOR AN ACYLOXY RADICAL INTERMEDIATE

Reported by Daniel E. Falvey

September 18, 1986

Acyloxy radicals, **1**, have been postulated as intermediates in a number of different reactions. For example, the electrochemical oxidation of carboxylic acids<sup>1</sup> (the Kolbe reaction) and the reactions of silver (I) carboxylates with halogens<sup>2</sup> (the Hunsdieker reaction) have been suggested to proceed through acyloxy radicals. Acyloxy radical intermediates have also been implicated in the thermal<sup>3</sup> and photochemical<sup>4</sup> decomposition reactions of peresters and diacylperoxides (Eq. 1).



The existence of the benzoyloxy radical, **1a**, has been suggested by chemical trapping experiments,<sup>5</sup> low-temperature ESR spectroscopy<sup>6</sup> and ab-initio calculations.<sup>7</sup> Evidence for the acetoxy radical, **1b**, has also been obtained from chemical trapping,<sup>8</sup> isotope labeling experiments,<sup>9</sup> and CIDNP observations.<sup>10</sup> Recent time-resolved ESR experiments by Yamauchi and co-workers showed the lifetime of benzoyloxy, **1a**, in liquid solution to be ca. 250 ns.<sup>11</sup> From the effect of solvent viscosity on the rate of acetyl peroxide thermolysis, the lifetime of acetoxy (**1b**) has been estimated to be ca. 1 ns at 60°C.<sup>12</sup>

Bartlett and co-workers studied the effects of structure on the thermal decomposition reactions of a series of peresters.<sup>13</sup> Their findings led to the suggestion that when a sufficiently stable radical was formed on decarboxylation (e.g. R=PhCH<sub>2</sub> or Ph<sub>2</sub>CH) that decarboxylation would occur simultaneously with O-O bond cleavage. Subsequent studies on isotope effects,<sup>14</sup> solvent viscosity dependence,<sup>15</sup> and volumes of activation<sup>16</sup> were largely consistent with this proposal.

The photochemistry of *tert*-butyl (9-methyl)fluorene-9-percarboxylate, **2c**, in liquid acetonitrile and cyclohexane has been investigated.<sup>17</sup> Photolysis of this perester in either solvent leads to the expected<sup>4a</sup> homolytic reaction products. The intermediacy of the 9-methyl-9-fluorenyl radical, **3c**, was



nanosecond time-scale laser spectroscopy. Picosecond laser irradiation of **2c** dissolved in acetonitrile or cyclohexane results in the formation of the 9-methyl-9-fluorenyl radical, **3c**. This species does not appear immediately, but rather it grows in by a first order process with  $k^{-1} = 55 \pm 15$  ps. This observation together with consideration of the photophysical properties of perester **2c**<sup>18</sup> suggest that the observed rise time represents the rate of decarboxylation of an acyloxy radical. If this interpretation is correct, this finding would imply that all acyloxy radicals have finite lifetimes even where R is a highly stabilized radical.

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# LIPOXINS: NEW METABOLITES OF THE 15-LIPOXYGENASE BRANCH OF THE ARACHIDONATE CASCADE

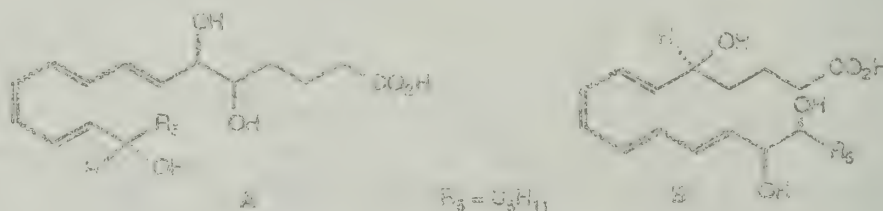
Reported by Marty Pomper

September 22, 1986

The prostaglandins, thromboxanes, and leukotrienes, are oxygenated derivatives of arachidonic acid which produce multitudinous physiological and pathological effects in mammals. These potent compounds are capable of eliciting such varied responses as peripheral bronchoconstriction in humans<sup>1</sup> and estrus synchronization in cows.<sup>2</sup> Understanding their roles in the immune system has motivated the majority of work in this field over the last twenty years.

The difference in anti-inflammatory activity displayed by aspirin and steroids prompted Samuelsson to investigate the production of pro-inflammatory metabolites of arachidonic acid which arise through a cyclooxygenase-independent mechanism.<sup>1,3</sup> Experiments involving polymorphonuclear leukocytes (PMNL, immunoregulatory cells) led to discovery of the leukotrienes.<sup>4</sup>

Recently,<sup>5,6</sup> Samuelsson isolated two non-polar lipxygenase products and determined their structures to be positional isomers of fully conjugated trihydroxytetraenes. He named these new metabolites "lipoxins" (LXs) because it was believed they were produced through multiple lipxygenase interactions (Figure 1).



Initial Structures of Lipoxins A and B

Figure 1.

## Elucidation of Skeletal Connectivity

Samuelsson found that by mimicking the sequence of reactions by which LXs are thought to be produced, by incubation of human PMNL with 15(S)-hydroperoxy-5,8,11Z,13E-eicosatetraenoic acid (15-HPETE) plus a divalent cation ionophore (A23187),<sup>7</sup> the yield of these new polar compounds could be enhanced several hundred fold.<sup>8,9</sup> This technique greatly facilitated the initial characterization of LXs, which was accomplished through UV spectroscopy, GC/MS, and chemical degradation.

Lipoxins A and B show UV absorptances at  $\lambda_{max}^{MeOH} = 301$  and 300 nm respectively. These values represent substantial bathochromic shifts compared

to most arachidonic acid metabolites; the leukotrienes, which possess a conjugated triene chromophore, absorb near 280 nm. A conjugated tetraene structure was proposed. Improved HPLC analysis has shown LXs A and B each to be mixtures of three isomers.<sup>10,11</sup> The presence of these additional isomers was not known during the stereochemical determination and is no doubt responsible in part for the controversy concerning LX stereochemistry.

Trimethylsilyl derivatives of LX methyl esters were prepared and subjected to GC/MS. Confirmation of the positions of the vicinal alcohol groups of LXA at C-5 and C-6 was provided by MS analysis of the n-butylboronate-Me<sub>3</sub>Si derivative; in addition to the molecular ion ( $m/z = 504$ ), a fragment at  $m/z = 173$  appeared. These positions were further substantiated by MS analysis of the products of catalytic hydrogenation of the silyl derivative. The S-configuration of the hydroxyl group at C-15 was established by oxidative ozonolysis of the (-)-menthoxycarbonyl derivative and comparison of the products to known standards by GC. Consideration of the configurational analysis, which indicates an allylic hydroxyl group at C-15, and the UV data, confines the conjugated tetraene chromophore between C-7 and C-14. With the skeletal structures in hand, the lipoxins were ripe for a more complete stereochemical determination. This was effected through total synthesis.

## Chemical Syntheses

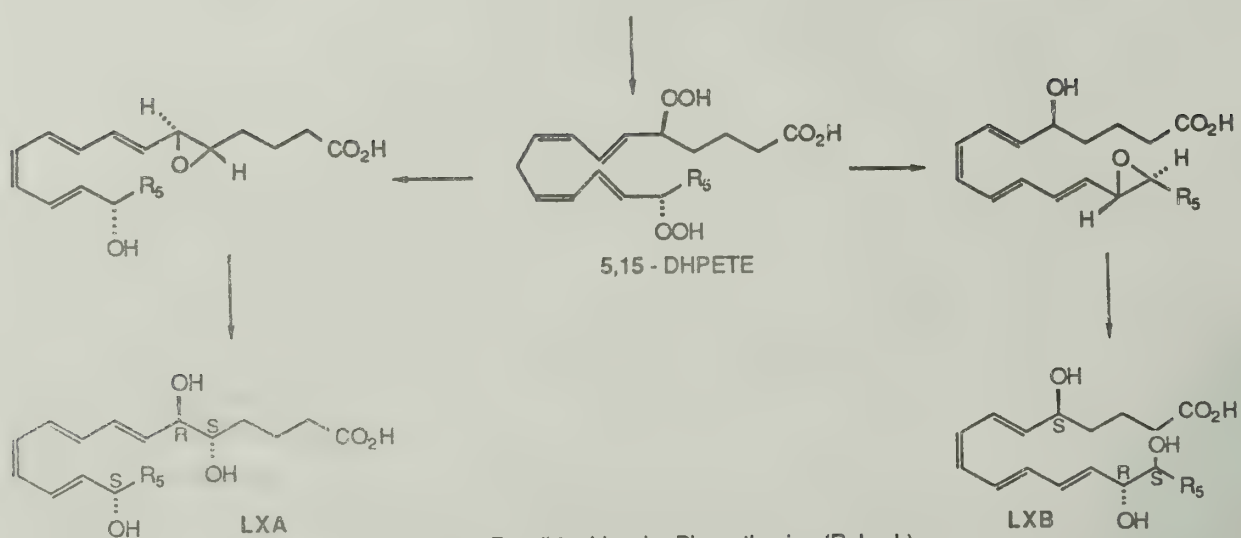
In addition to the intriguing stereochemical uncertainties remaining, the syntheses of the LXs was pursued because of the minute quantities available from natural sources; two liters of human blood provided less than 1 $\mu$ g of LXA.<sup>12</sup> A more efficient means of obtaining pure material was desired in order to perform biosynthetic and biological studies.

Although it has been less than three years since the initial report describing LXs,<sup>5</sup> several elegant syntheses have been reported.<sup>13</sup> As with leukotrienes, variations of three basic approaches have been applied:<sup>4b</sup> biomimetic syntheses from arachidonic acid metabolites, elaboration of carbohydrate precursors for asymmetric syntheses, and use of simple olefin and alcohol precursors.

Synthetic work initially concentrated on LXA. After consideration of the likely biosynthetic route to lipoxins (Scheme I), Rokach used a biomimetic approach in the first LX synthesis.<sup>12,13a</sup> They reasoned that LXs may arise through opening of an unstable epoxide intermediate, in analogy to the formation of leukotrienes from LTA<sub>4</sub>.<sup>14</sup> The epoxide was thought to be formed via stereospecific proton abstraction from C-10 of 15-HPETE to give 5,15-DHPETE, a previously characterized compound;<sup>15</sup> enzymatic dehydration follows. A convergent synthesis of the purported tetraene epoxide intermediate was

## Scheme I

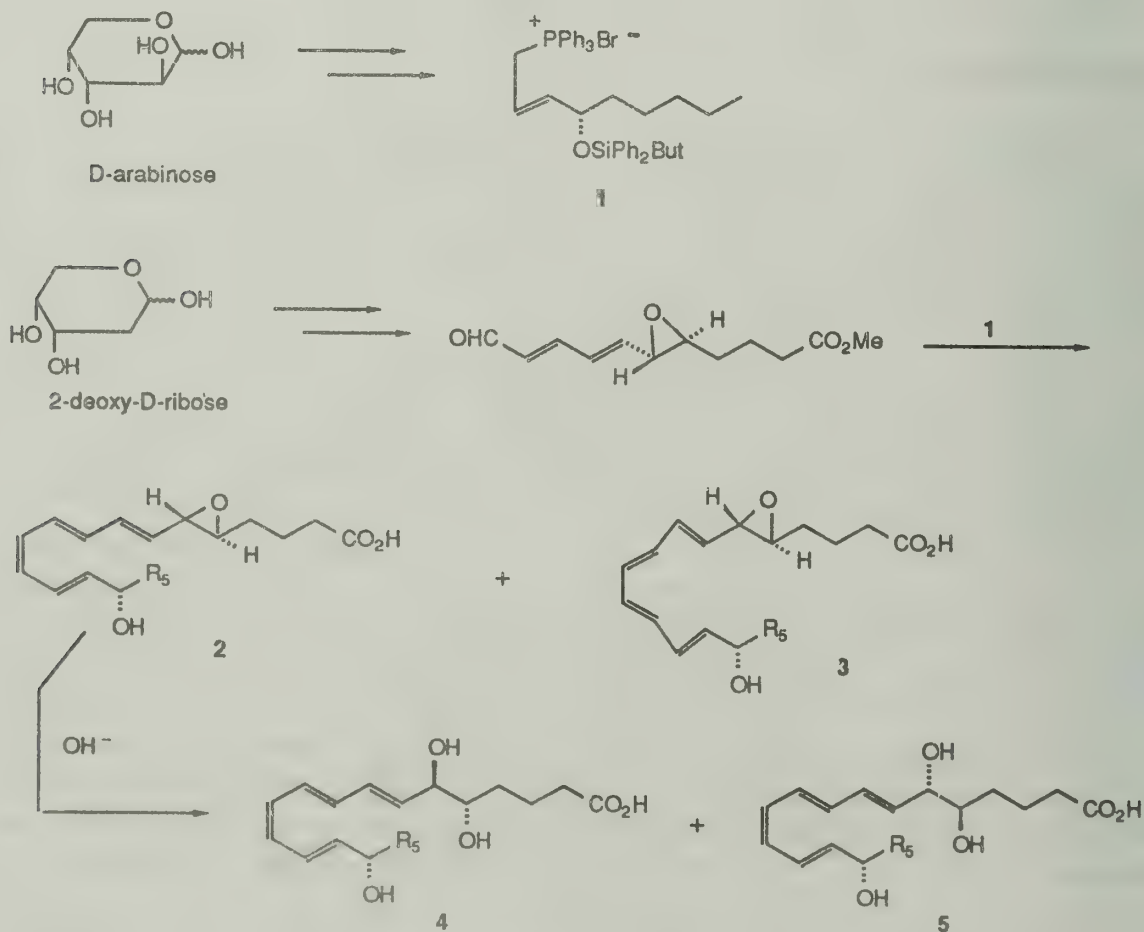
15-HPETE



Possible Lipoxin Biosynthesis (Rokach)

undertaken. Carbohydrate precursors were used as stereochemical pivots for the three hydroxyl stereocenters (Scheme II). Nucleophilic  $S_N2$  opening of epoxides

## Scheme II

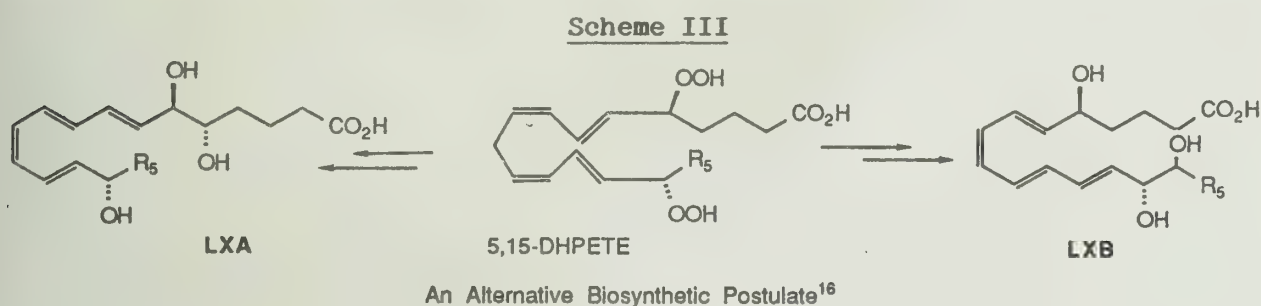


Rokach's Synthesis of Lipoxins A



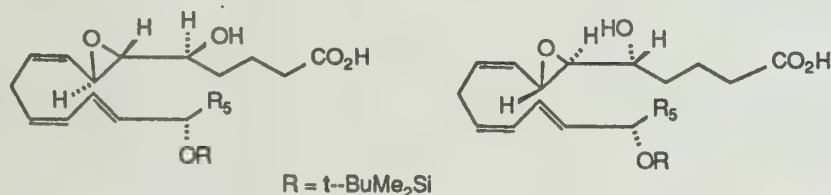
2 and 3 at the more electrophilic position (C-6) gave the corresponding (5S, 6R, 15S) LXs A. Only products of the 11Z epoxide are shown. Internal carboxylate displacement, with subsequent hydrolysis of the lactone, produced the corresponding (5R, 6S, 15S) diastereomers. Epoxides 2 and 3 were produced in a 2:1 ratio and trihydroxytetraene 5 was later determined to be the major product. Comparison of these four synthetic isomers with natural material was not carried out; however, it will later be shown that (5S, 6R, 15S) represents the natural stereochemistry.

The second synthetic effort by this team was directed toward a series of LXA isomers of known stereochemistry for comparison to natural material.<sup>13b</sup> Biogenetic considerations again dictated the choice of targets. In addition to the route shown in Scheme I, a second biosynthetic postulate, involving an unprecedented third lipoxygenation, was envisioned (Scheme III).



These two modes of biosynthesis together generate three possible structures for LXA: (5S, 6R or S, 15S, 11E), (6R, 11Z), and the corresponding three for LXB. Two new methods for LXA synthesis were realized. The first utilized  $LTA_4$  (5S, 6S, 15S) as starting material which was converted to LXA isomers in three steps, two chemical and one enzymatic. Synthetic  $LTA_4$  isomers were made: epimeric at C-5, C-6, or both C-5 and C-6. These synthetic isomers were then converted into their corresponding trihydroxytetraenes. The second new synthetic method relied on carbohydrate precursors and confirmed the absolute stereochemistry of the  $LTA_4$  derived compounds.

With unambiguous standards, determination of the absolute stereochemistry of natural LXA was possible. The authors prepared natural material according to Samuelsson<sup>6</sup> and found only their (5S, 6S, 15S, 11Z) isomer to co-migrate, both as the free acid and as the methyl ester, on RP-HPLC. Lipoxin A was concluded to have the stereochemistry epimeric at C-6 to that shown in Schemes I and III.

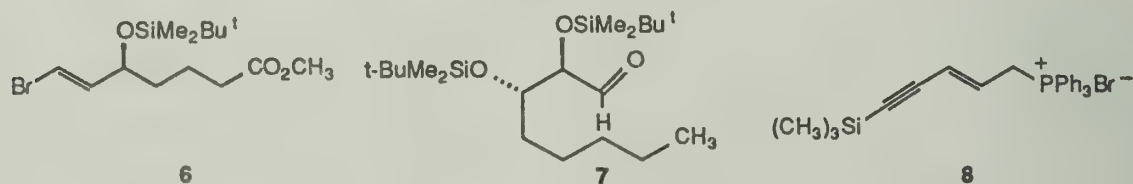


Intermediates in Corey's Lipoxin A Synthesis

Figure 2

By taking advantage of vanadium (V)-catalyzed epoxidation, Corey was able to generate all four  $15S$  diastereomers of LXA.<sup>13c</sup> The synthesis commences with the methyl ester of  $15(S)$ -hydroxy-5,8,11 $Z$ ,13 $E$ -eicosatetraenoic acid (15-HETE), and proceeds through epoxy alcohol intermediates. Erythro epoxy alcohols are the favored products of vanadium (V)-catalyzed allylic alcohol epoxidation,<sup>17</sup> and erythro was formed 2:1 over threo in this instance. The threo intermediates are shown in Figure 2. A similar sequence was applied to the erythro epoxy alcohol diastereomers to generate the ( $5S$ ,6 $R$ ,15 $S$ ) and ( $5R$ ,6 $S$ ,15 $S$ ) trihydroxytetraenes. Comparison of natural LXA with synthetic standards led Corey to the same conclusion as Rokach, namely, that LXA has the ( $5S$ ,6 $S$ ,15 $S$ ) stereochemistry.

Nicolaou applied Pd(0)-Cu(I) catalysis to couple a terminal acetylene with an appropriate bromoalkene in the key reaction in his sequence to LXA.<sup>13g,18</sup> With natural LXA presumed to be well characterized, attention was trained on LXB which had stereochemical ambiguities concerning the geometry of the 8,9-double bond and the hydroxyl group at C-14. The  $S$ -oriented dioxygenation known to occur for 5-lipoxygenase implied a  $5S$  configuration.<sup>19</sup> The first total synthesis of LXB<sup>13d,i</sup> utilized Pd(0)-Cu(I)-catalyzed coupling and was recently expanded to encompass six LXB isomers:  $8E$  and  $8Z$ , ( $14S$ ,15 $S$ ), ( $14S$ ,15 $R$ ), ( $14R$ ,15 $S$ ). A highly convergent approach was taken, conscripting the Sharpless epoxidation to control the stereochemistry of the vicinal diol and using selective hydrogenation to establish the  $8Z$  geometry. Figure 3 depicts the



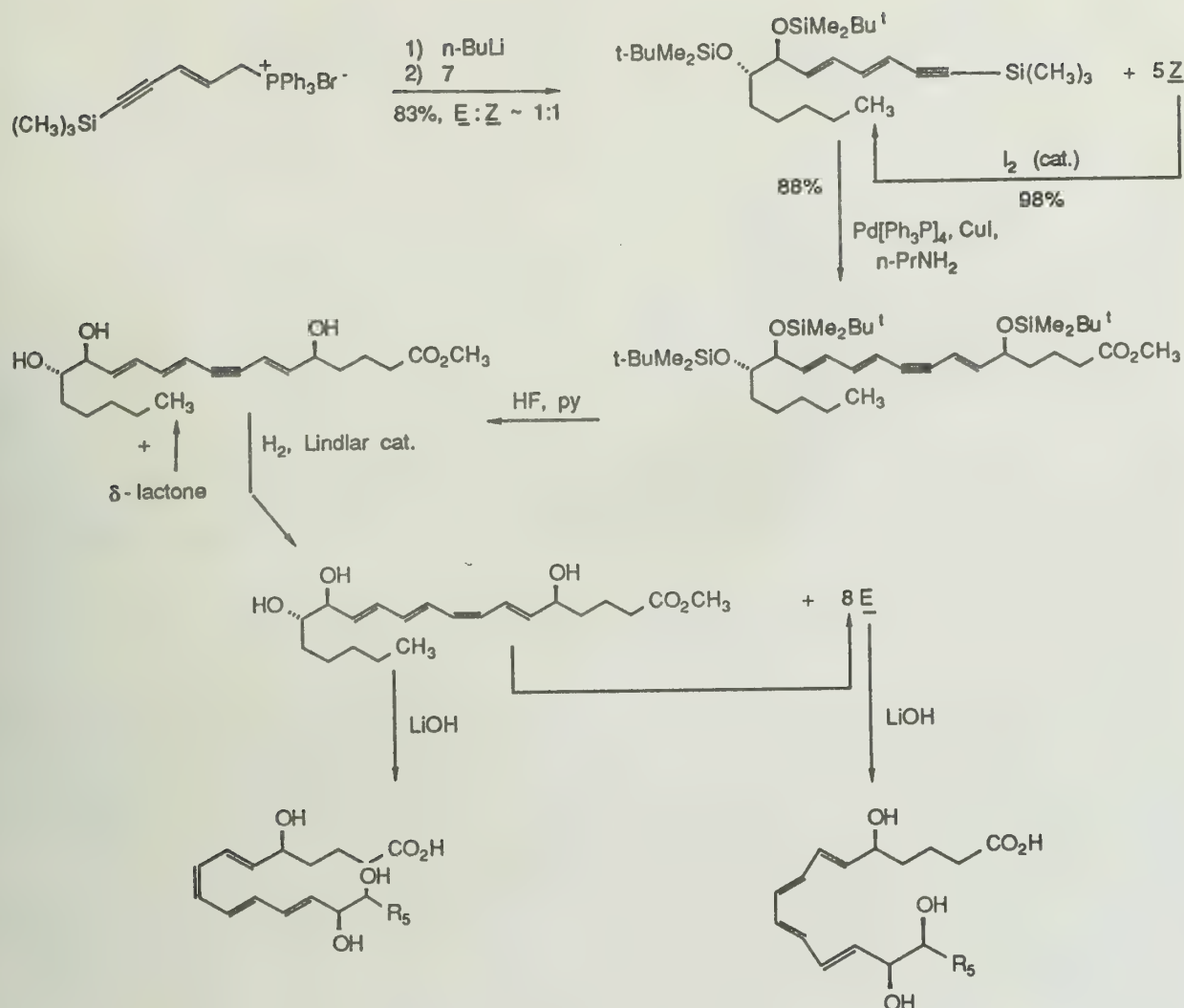
Subtargets for Nicolaou's Lipoxin B Synthesis

Figure 3

component subtargets, while Scheme IV outlines their consolidation. By starting with the  $E$ -isomer of the alcohol which led to **7** and by using both (+) and (-)-diethyl tartrate, Nicolaou synthesized the remaining isomers.

Although synthetic isomers of LXB are available, the stereochemistry of the natural compound is still debated. Rokach adapted his carbohydrate-based LXA synthesis (*vide supra*) to LXB.<sup>13e</sup> They determined LXB to consist of the all trans C-14 epimers.<sup>20</sup> Corey, on the other hand, proposed the  $14S$ ,15 $S$ ,8 $Z$  stereochemistry for the natural compound. Both groups prepared their own natural LXB for comparison. Rokach responded to Corey's stereochemical assignment with biosynthetic studies and examination of their synthetic and natural LXB isomers using Corey's HPLC conditions.<sup>21</sup> Both on mechanistic grounds and through HPLC re-examination, he stood by his original assignment. Corey later retracted his original proposal, after re-isolation and comparison of LXB, and corroborated the findings of Rokach.<sup>13j</sup>

## Scheme IV



Synthesis of (5S, 14S, 15S) Lipoxins B (Nicolaou)

Most recently, Morris, using carbohydrate based methodology employing an epimerization reaction to obtain C-14 epimers of 8E and 8Z LXB, assigned yet another stereostructure to the natural product.<sup>13h</sup> They, however, used material prepared by the original investigators as the basis for their assignment. They claim natural LXB to be composed of three components: 14S all trans, 14R all trans, and (14R, 8Z) in a ratio of 3:5:2. The authors state that isomerization of the (14R, 8Z) compound occurs to a certain extent during isolation, explaining its absence in the isolates of Rokach; however, they could not account for the (14S, 8Z) isomer, seen by Corey. This latest assignment receives further support from recent biological and biosynthetic studies; interestingly, only the (14R, 8Z) isomer was able to activate protein kinase C.<sup>11</sup>



## Biosynthesis

Two biosynthetic postulates have been entertained, and were briefly mentioned earlier in this report. The second postulate (Scheme III), hypothesizing three independent lipoxygenations, was dispatched in short order, although for what now appear to be the wrong reasons.<sup>12</sup> This idea was premised on the proven ability of at least two consecutive lipoxygenations to occur in PMNL.<sup>6,16</sup> Essentially, a carbon-centered radical at C-10 is formed prior to vinylogous trapping of molecular oxygen at C-6 or at C-14; reduction of the intermediate hydroperoxides would give LXA or B, respectively.<sup>22</sup> The 11 $\underline{Z}$  LXA and 8 $\underline{Z}$  LXB isomers should result from this pathway. Also, a previous example implies the stereochemistry of the third lipoxygenation to give the  $\underline{R}$ -alcohol in each case.<sup>23</sup> Lipoxins A and B should therefore have the stereochemistries shown in Scheme III. Because the (5 $\underline{S}$ ,6 $\underline{R}$ ,15 $\underline{S}$ ) LXB isomer represented an insignificant fraction of their total isolate and the corresponding 14 $\underline{R}$  LXB was entirely absent, Rokach dismissed this postulate. Ironically, these two natural isomers were recently determined to be the only ones to exhibit significant biological activity.<sup>11</sup>

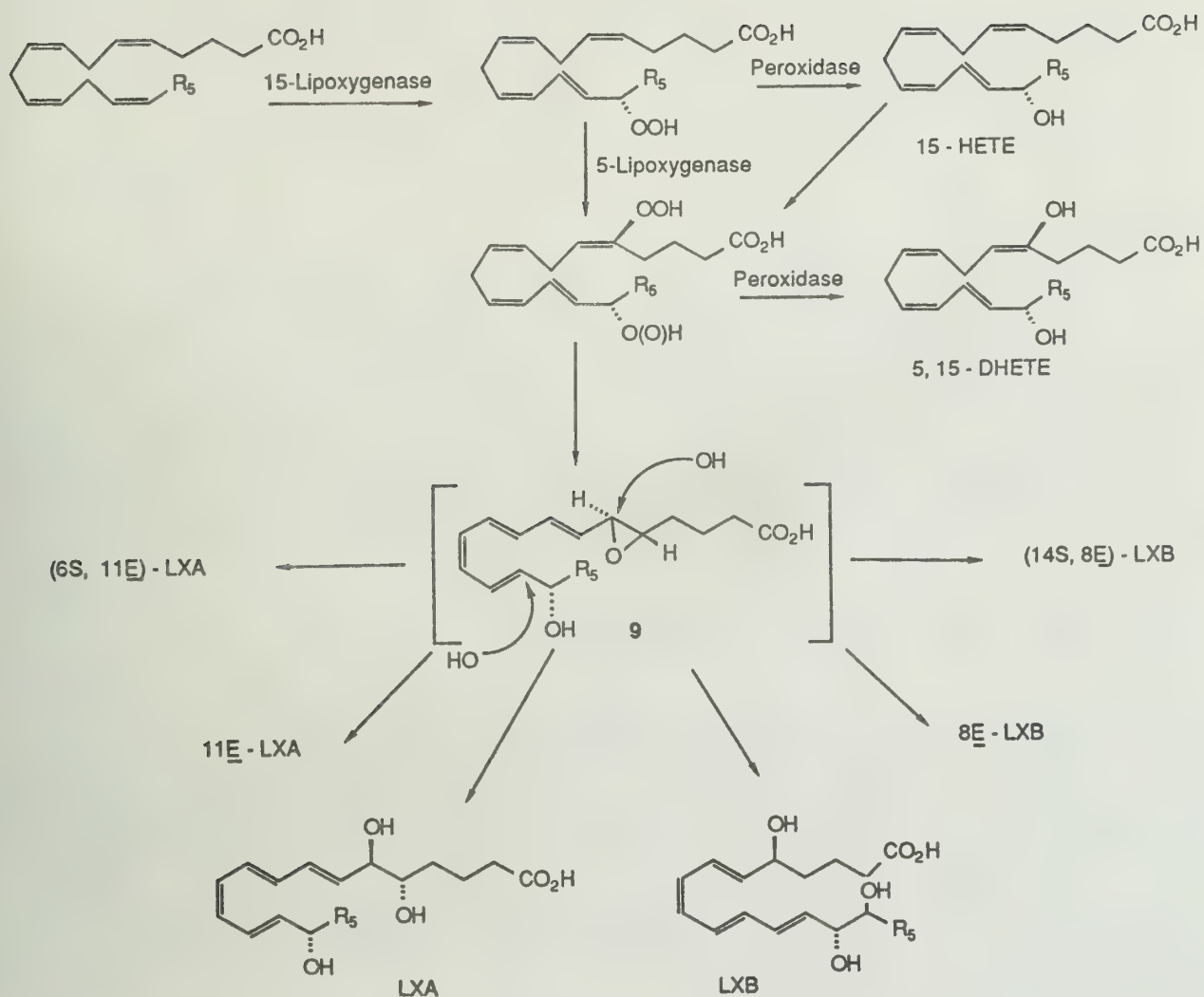
A triple lipoxygenation mechanism was refuted in two experiments by Serhan (Samuelsson group).<sup>11,24</sup> The first involved incubation of either 15-HPETE or 15-HETE with A23187 in the presence of an  $^{18}\text{O}_2$ -enriched atmosphere. By MS analysis it was shown that only the oxygen at C-5 was derived from molecular oxygen in the compounds isolated (LXs B and 5,15-DHETE). Lipoxygenase inhibitors were used in the second experiment. Eicosatetraynoic acid (ETYA), a 12-lipoxygenase substrate analogue, had no effect on LXA or B synthesis in leukocytes. Another biosynthetic mechanism must be sought.

The first biosynthetic postulate, as initially proposed, is shown in Scheme I. It suggests an unstable tetraene epoxide intermediate and finds precedent in leukotriene formation. Rokach proposed the nucleophilic epoxide opening mechanism, but concluded that it proceeded by a non-enzymatic process.<sup>21</sup> His experiments are inconclusive, however, because it is uncertain whether or not synthetic **9** (Scheme V) actually enters the leukocytes on incubation.<sup>11</sup>

The tetraene epoxide intermediate was strongly implicated in work by Serhan.<sup>11,12,24</sup> Several lines of evidence support this claim. 15-HETE was shown to serve as a precursor to all LXs. Since 15-HETE is not expected to form a 14,15-epoxide, it likely gives rise to the LXs through a 5,6-epoxide after 5-lipoxygenation. The  $^{18}\text{O}$  incorporation pattern is consistent with an epoxide intermediate (*vide supra*). The absolute stereochemistry of the products could be explained by enzymatic nucleophilic epoxide opening. In fact, tetraene epoxide **9**, when incubated with liver cytosolic epoxide hydrolase, gave rise to natural lipoxin A to the exclusion of the 6 $\underline{S}$  diastereomer. In view of these data, the biosynthesis of LXs is outlined in Scheme V.



Scheme V



Lipoxin Biosynthesis (Serhan)

## Biological Activity

Lipoxins A and B are active against natural killer (NK) cells ( $IC_{50} \sim 10^{-7}$  M) which may participate in immune surveillance.<sup>11,25</sup> Lipoxin A has spasmogenic capabilities. These two properties comprised the bioassays used to prove the stereochemistry of natural LXA.<sup>10</sup> Only the 6R isomer was active in either assay, demonstrating the remarkable specificity of the biological response.

Mast cell degranulation and superoxide anion generation<sup>26</sup> in PMNL have been shown to be enhanced by LXA; however, LXA is one hundred times less potent than  $LTB_4$  at provoking degranulation.<sup>11</sup>

Lipoxins A and B both activate protein kinase C,<sup>27</sup> although B is ten times less potent and its isomers are ineffective. Lipoxin A was ~ 30 times more potent than diacylglyceride, another putative activation signal for protein kinase C.<sup>11,28</sup> The LXs therefore may regulate enzyme activity in addition to serving as immunoregulators.

## Conclusions

The lipoxins represent a colorful addition to the arachidonate cascade. Their structures and mode of biosynthesis have been the subject of much debate. Recent methodology has been employed in their total syntheses. They potentially have far reaching biological effects which may be beneficial or detrimental to the organism. Further biological studies are required to ascertain the activity of these compounds in vivo at physiological concentrations. In this manner their roles in certain disease processes, if significant, can be more carefully defined and a program of selective inhibitor development can be initiated.

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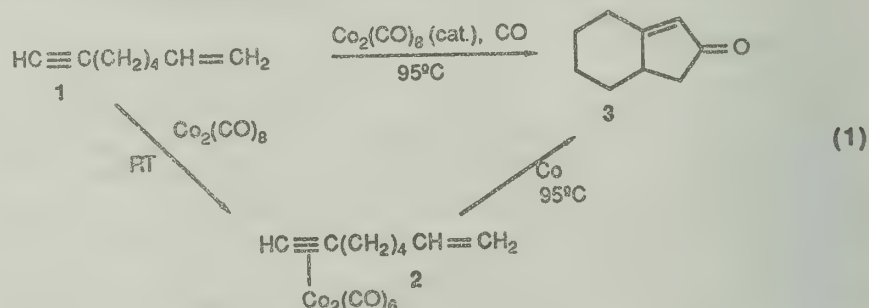
## SYNTHETIC UTILITY OF ALKYNE-DICOBALT HEXACARBONYL COMPLEXES

Reported by Kevin Pinney

September 29, 1986

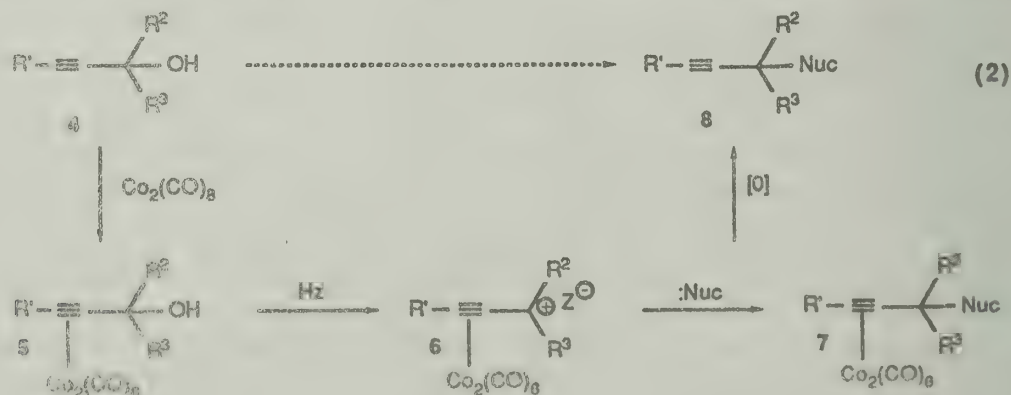
The reaction of an alkyne with octacarbonyldicobalt generates a very stable complex of the general formula  $(RC_2R')Co_2(CO)_6$ .<sup>1</sup> The complex may be formed from a variety of both terminal and internal alkynes, including cyclic alkynes, diynes, and triynes, and tolerates a wide array of substituents, including halogen, ether, ester, alkyl, vinyl, aryl, silyl, and others. Synthetically, these complexes are of great value, not only as protected forms of the triple bond,<sup>2</sup> but more importantly as a facile means of generating the cyclopentenone structure, which is commonly found in natural products.

As first reported by Pauson and Khand in 1973, the reaction involves a cobalt carbonyl-promoted cocyclization of an alkyne and an alkene.<sup>3</sup> The reaction is promoted when strained alkenes such as norbornadiene are used: however, with unstrained alkenes it requires forcing conditions and affords ketones in low yield.<sup>4</sup> Schore and co-workers, however, have found that an intramolecular version of the reaction which utilizes  $\alpha,\omega$ -enynes affords the cyclopentenones in moderate yield under relatively mild conditions (Eq. 1).<sup>5</sup>



The reaction is easily effected by employing a catalytic amount of octacarbonyldicobalt under a carbon monoxide atmosphere.<sup>6</sup> The intramolecular version of this reaction provides a convenient route to dl-coriolin.<sup>7</sup>

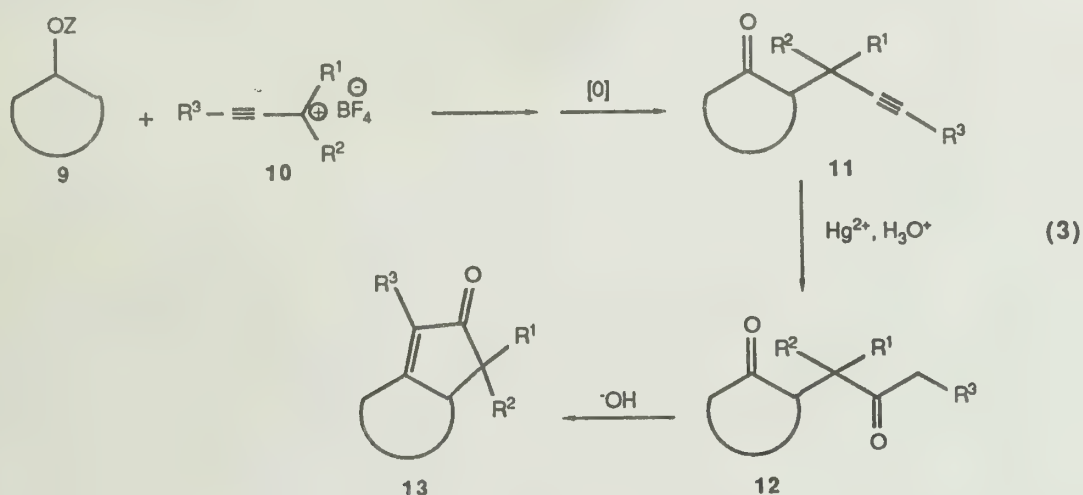
Cobalt-complexed propargyl cations (6) have recently received much attention as electrophilic propargyl synthons (Eq. 2).<sup>8</sup> The complexes couple





with arenes,<sup>9</sup>  $\beta$ -dicarbonyl compounds,<sup>10</sup> ketones and enol derivatives,<sup>11</sup> allyl silanes,<sup>12</sup> and trialkynyl alanes.<sup>13</sup> These coupling reactions provide an efficient method for introducing the propargyl moiety without forming allenic byproducts, which often occurs with conventional propargylation techniques.<sup>14</sup> In addition, the facile introduction<sup>15</sup> and removal<sup>16</sup> of the cobalt occurs under mild conditions, making these cationic complexes especially attractive as propargyl equivalents for carbon-carbon bond formation. For compounds which are sensitive to protic acids, cobalt-complexed propargylic ethers readily undergo heterolysis of the alkoxy group in the presence of Lewis acids, thereby becoming effective alkylating agents.<sup>17</sup>

The cobalt-mediated cyclopentenone annulation is a novel and useful application of these complexes in synthesis. The annulation entails successive propargylation, demetalation, regiospecific hydration, and base-catalyzed cyclization (Eq. 3).<sup>18</sup> Application of this method to natural product synthesis has led to very efficient syntheses of dihydrojasmonone<sup>19</sup> and cyclocolorone.<sup>20</sup>



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## ASYMMETRIC CYCLOPROPANATIONS

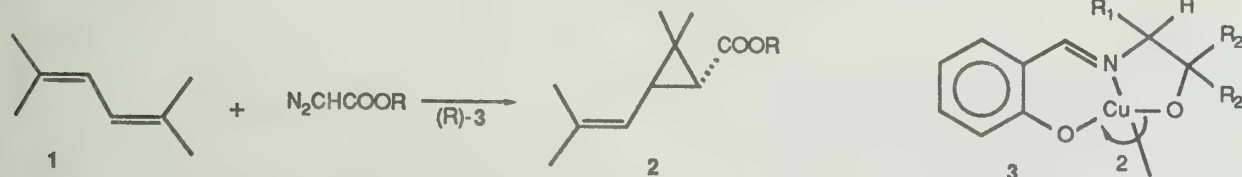
Reported by Kris Deming

October 23, 1986

There has been much interest in asymmetric cyclopropanation for the synthesis of natural products and pyrethroid acid insecticides.<sup>1</sup> Chiral natural products generally occur naturally in one enantiomeric form and the absolute stereochemistry of the pyrethroid acid insecticides is very important in determining their activity. Early attempts to achieve asymmetric cyclopropanations met with only limited success (8-9% ee),<sup>2,3</sup> but these results sparked interest in many other groups.

## Metal Carbenoid Cyclopropanations

The most widely used method involves cyclopropanation of olefins with alkyl diazoacetates in the presence of chiral transition metal complexes.<sup>4</sup> Studies were undertaken by Aratani to find the optimum catalyst and alkyl diazoacetate to produce the highest optical yield and trans/cis ratio in the formation of alkyl chrysanthemate (2) from 2,5-dimethyl-2,4-hexadiene (1). Salicylaldehyde imine complex 3 (R configuration),<sup>5a</sup>  $R_1$  = methyl and  $R_2$  =



5-*t*-butyl-2-(*n*-octyloxy)phenyl was the most effective catalyst found, and 1-menthyl diazoacetate was the best of the diazoacetates tried.<sup>5b</sup> Thus, cyclopropanation of the diene (1) with 1-menthyl diazoacetate in the presence of (R)-3 gave (1R)-trans chrysanthemate with 93% trans selectivity and 94% ee. Some examples utilizing this procedure are given in Table I.

Table I. Asymmetric cyclopropanation using copper complex 3 and alkyl diazoacetate<sup>b</sup>

Olefin	Cat. <sup>c</sup> Conf.	Product cis/trans	% ee		Conf.	
			cis	trans	cis	trans
Styrene	S	18/82	78	81	1R,2S	1R,2R
trans-4-Octene	S			84		2R,3R
1,1-Diphenylethylene	R			75		1S
2,5-Dimethyl-2,4-hexadiene	R	7/93	a	94	1R,3S	1R,3R
Isobutylene	R			92		1S
2-Methyl-5,5,5-trichloro-2-pentene	S	85/15	91	11	1R,3R	1R,3S

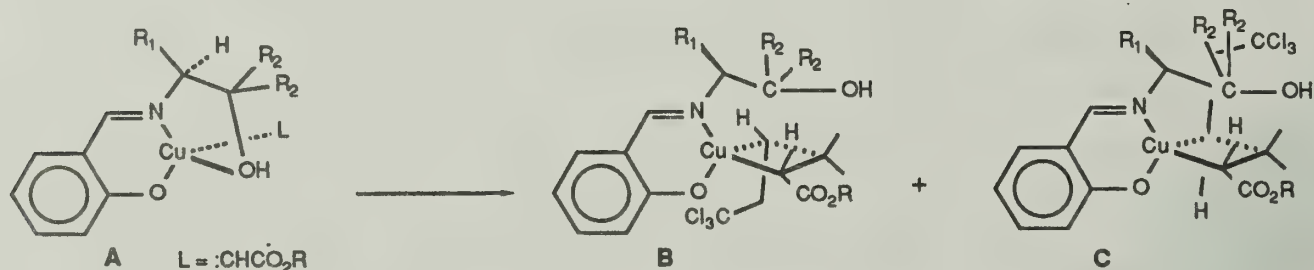
a) The optical purity could not be determined because resolution was not complete.

b) (1)-Menthyl diazoacetate was used for the first four and ethyl diazoacetate for the last two.

c) Catalyst 3 had  $R_1$ =methyl and  $R_2$ =5-*t*-butyl-2-(*n*-octyloxy)phenyl except in the case of isobutylene where  $R_1$ =benzyl and  $R_2$ =2-(*n*-butoxy)-5-*t*-butylphenyl.

Fig. 1 shows the intermediates in the mechanism proposed by Aratani to account for the asymmetric induction seen under these conditions.<sup>5d</sup> The mechanism is shown for the reaction of ethyl diazoacetate with 5,5,5-trichloro-

2-methyl-2-pentene in the presence of the catalyst (S)-3. A copper-carbene complex is formed (A- Fig. 1) in which the carboxylate is directed downward owing to the steric effects of the other copper ligands. Attack of the olefin from the back side of the plane gives metallocyclobutanes B and C. Upon collapse of B and C, the cis and trans cyclopropanes are formed with geometry transferred from the metallocyclobutane intermediates. The configurational and enantiomeric excesses depend on the configuration of the catalyst and the nature of the olefin.



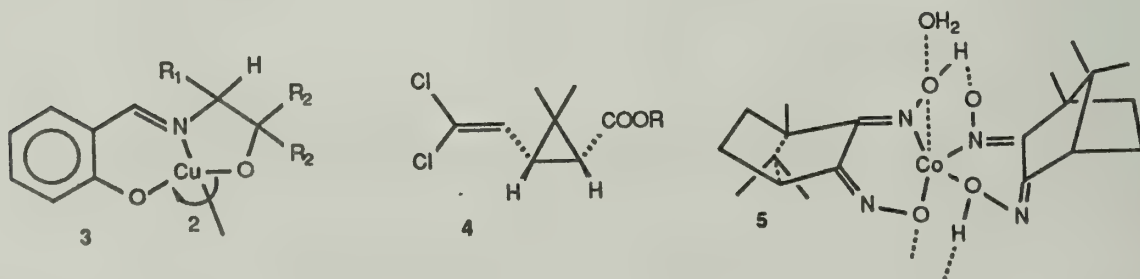
Intermediates in the mechanism proposed by Aratani for asymmetric cyclopropanation with salicylaldehyde imine complex 3 ( $R_1 = \text{Me}$ ,  $R_2 = 5\text{-}t\text{-Butyl-2-(n-octyloxy)phenyl}$ ).

Figure 1

Milner also used chiral Schiff base-copper complexes of amino alcohols for asymmetric induction in the formation of cyclopropane carboxylates.<sup>6</sup> Ethyl diazoacetate was decomposed by the catalyst in the presence of olefins in an attempt to form (1R)-cis-permethrinic carboxylate (4). The chemical yields obtained were between 3 and 49%, the best cis/trans ratio was 80/20 (most were near 50/50), and the best optical yield was 44% for (1R)-cis.

Optically active bornyl, menthyl, or 2-methyl-1-butyl diazoacetate with cuprous chloride in the presence of styrene gave cyclopropyl esters in yields of >90%, trans/cis ratios between 2.2 and 2.9, and optical yields between 0 and 12%.<sup>7</sup>

Nakamura and co-workers found bis[(-)-camphorquinone-9-dioximato] cobalt II ( $\text{Co}(\alpha\text{-cqd})_2$  - 5) to be the most active of the many chiral metal complexes they examined.<sup>8a,4</sup> Chemical yields of 80-95% and optical yields exceeding 80% were obtained using  $\text{Co}(\alpha\text{-cqd})_2$  (5) in the formation of optically active cyclopropanes



(Table II).<sup>8b-d,9</sup> A direct correlation was found between the bulk of the ester alkyl group of the diazoacetate and the optical yield and the trans/cis ratio. The catalyst was utilized at the level of 1-3 mol% in neat olefin. Only

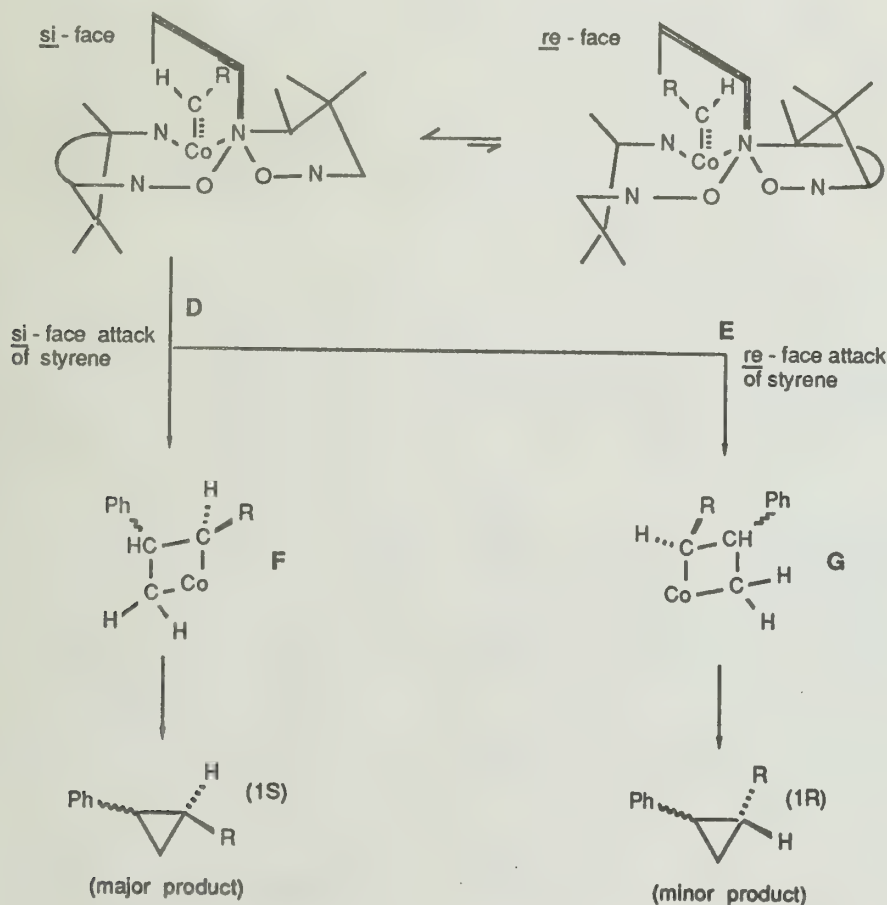


terminal double bonds conjugated with a vinyl or aryl group gave significant results under these conditions. Reduced optical and chemical yields were obtained with acrylonitrile and acrylate esters. The (1S) enantiomer was always obtained in excess.

Table II. Asymmetric cyclopropanation using cobalt complex **5** and ethyl diazoacetate

Olefin	% Yield	% ee ( $[\alpha]_D$ )		Conf.	
		cis	trans	cis	trans
Styrene	92	67	75	1S,2R	1S,2S
1,1-Diphenylethylene	95	--	70	--	1S
Methyl acrylate	11	--	33	--	1S,2S
trans-1-Phenyl-1,3-butadiene	92	(-13.8)	(+213)	--	--

The proposed mechanism for enantioselective cyclopropanation by  $\text{Co}(\alpha\text{-cqd})_2$  is shown in Fig. 2.<sup>8e</sup> First a cobalt-diazoacetate complex is formed which upon loss of nitrogen gives rise to a cobalt-carbene complex. Two conformations of the cobalt-carbene complex are possible (**D** and **E**) with **D** being the sterically preferred conformation. Preferential *si*-face attack of the olefin on **D** would give the cobaltacyclobutane **F**. Upon cyclopropane formation from complex **F**, the *S*-configuration at C-1 is obtained.

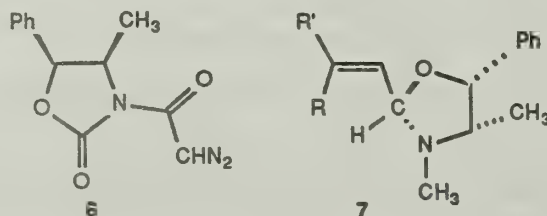


Mechanism proposed by Nakamura for asymmetric cyclopropanation with  $\text{Co}(\alpha\text{-cqd})_2$  (**5**).

Figure 2

Reaction of styrene with diazodimedone and chiral copper complexes of 3-(trifluoroacetyl)camphor gave cyclopropyl esters with optical yields of 73-100% and chemical yields of 21-48%.<sup>10</sup> A derivative of this catalyst was immobilized by bonding to silica gel. A chemical yield of 43% and an optical yield of 98% were obtained with this immobilized catalyst.

Cyclopropanation of styrene with the chiral N-diazoacetyl oxazolidone **6** (and a similar chiral diazo oxazolidone) using rhodium (II) acetate as a catalyst gave the corresponding cyclopropanecarboxamide which was converted to the ethyl ester without purification.<sup>11</sup> Chemical yields of 35-40%, optical yields of 13-14% (1R-configuration), and a trans/cis ratio of 1.8 were obtained.



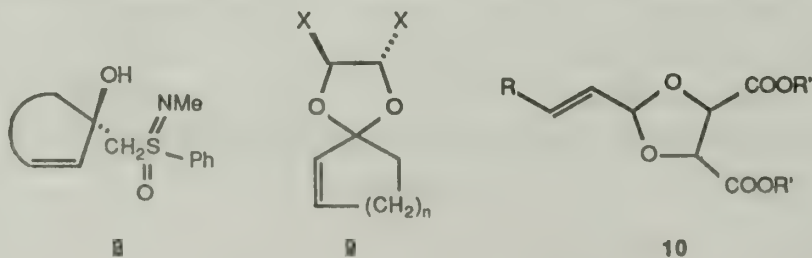
Reaction of vinyl oxazolidine **7** with diazomethane catalyzed by palladium acetate or with diazoisobutane and irradiation afforded the corresponding cyclopropanecarboxaldehyde products after hydrolysis in greater than 90% optical yield.<sup>12</sup> The oxazolidine was prepared by reaction of the corresponding conjugated aldehyde with (-)-ephedrine.

Brunner tested 37 catalysts in the reaction of 1,1-diphenylethylene and ethyl diazoacetate. Most of the catalysts were generated in situ, but some were isolated Copper complexes.<sup>13</sup> The best optical yield obtained was 60%.

### Simmons-Smith Cyclopropanations

Addition of anions of optically active sulfoximines to  $\alpha,\beta$ -unsaturated ketones gave  $\beta$ -hydroxysulfoximines (**8**) as two major diastereomeric adducts.<sup>14,15</sup> The diastereomers were separated by column chromatography and subjected to the Simmons-Smith reagent to give the corresponding diastereomeric cyclopropyl derivatives. Owing to the oxygen directing effect in the Simmons-Smith reaction, the cyclopropanation occurs cis to the hydroxyl group. The sulfoximine addition was reversed under mild thermolysis conditions to give the cyclopropyl ketone and starting sulfoximine. Both enantiomers of the cyclopropyl ketone can be obtained with optical purities of greater than 94%. Both cyclic and acyclic  $\alpha,\beta$ -unsaturated ketones give good optical yields with this procedure.

Mash described a different procedure to achieve asymmetric cyclopropanation of unsaturated cyclic ketones. A chiral ketal was formed (**9**-X=CH<sub>2</sub>OCH<sub>2</sub>Ph) in

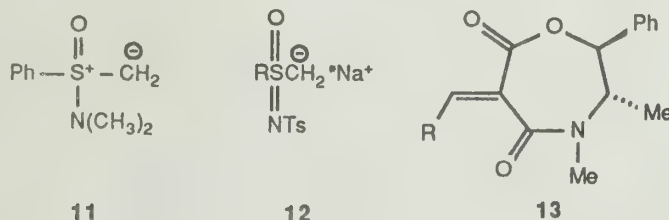


which one of the oxygens of the ketal preferentially directed the Simmons-Smith reagent.<sup>16</sup> The ketals were then hydrolyzed to the cyclopropyl ketones which exhibited optical purities of 70-90%. Yamamoto used chiral acetals (10) to bring about asymmetric induction in the reaction of the Simmons-Smith reagent with  $\alpha,\beta$ -unsaturated aldehydes.<sup>17</sup> Optical yields of 85-94% and chemical yields of 50-95% were obtained. Asymmetric cyclopropanation of menthyl and bornyl fumarates by the Simmons-Smith procedure generally gave low chemical and optical yields.<sup>18</sup>

### Asymmetric Cyclopropanations Using Enolates

Johnson utilized chiral oxosulfonium ylides (11)<sup>19a-d,f</sup> and chiral sulfoximine anions (12)<sup>19e</sup> for asymmetric induction in the formation of optically active cyclopropanes.<sup>15</sup> Both types of reagents proceed by conjugate addition to activated alkenes followed by nucleophilic displacement of the chiral sulfur group to form the cyclopropanes. Because of this Michael addition mechanism, olefins conjugated with an electron withdrawing group are required. The optical yields ranged between 12 and 49% for the two types of chiral reagents.

High optical yields (>90%) were obtained in the cyclopropanation of exocyclic alkylidene derivatives of optically active oxazepinediones (13) with dimethyl sulfoxonium methylide.<sup>20</sup> Hydrolysis of the cyclopropyl oxazepinediones followed by esterification with diazomethane gave the optically active cyclopropyl diesters.

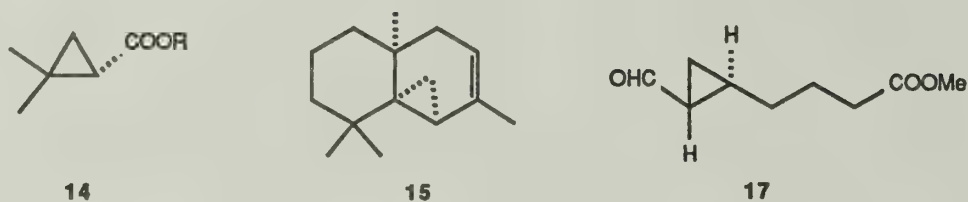


Reaction of bromochloromethane with the dienolate anion of di-(1)-menthyl succinate generated in situ gave trans cyclopropane dicarboxylate with 99% optical yield.<sup>21</sup>

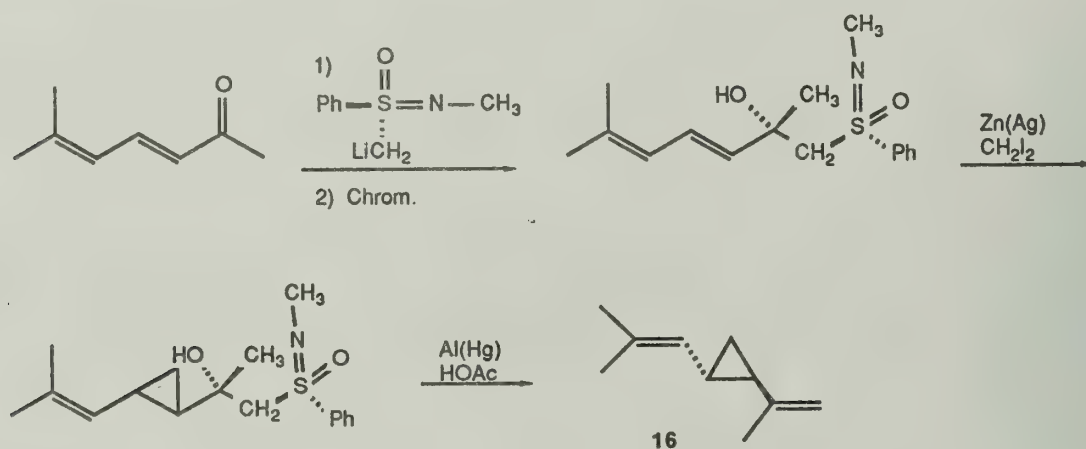
### Applications of Asymmetric Cyclopropanations

As mentioned earlier in the text, Aratani synthesized (1R,3R)-trans-chrysanthemic acid with a 94% ee.<sup>5b,22</sup> In contrast to this, the (1R)-cis isomer of permethrinic acid (4)<sup>5c</sup> was produced, using ethyl diazoacetate, 5,5,5-trichloro-2-methyl-2-pentene, and complex (S)-3 followed by base hydrolysis, in 91% ee and a cis/trans ratio of 85/15 (Table I). Cyclopropylcarboxylate 14 is a key intermediate in the production of Cilastatin, an enzyme inhibitor for dehydropeptidase I which is co-administered with the  $\beta$ -lactam antibiotic Imipenem (MK-0787).<sup>5d</sup> Cyclopropyl ester 14 was formed in 92% ee by reaction of isobutylene with ethyl diazoacetate catalyzed by complex (R)-3, a reaction which has been conducted on commercial scale. The

substituents on the catalyst ((R)-3) in this case were  $R_1$  = benzyl and  $R_2$  = 2-(n-butoxy)-5-t-butylphenyl).



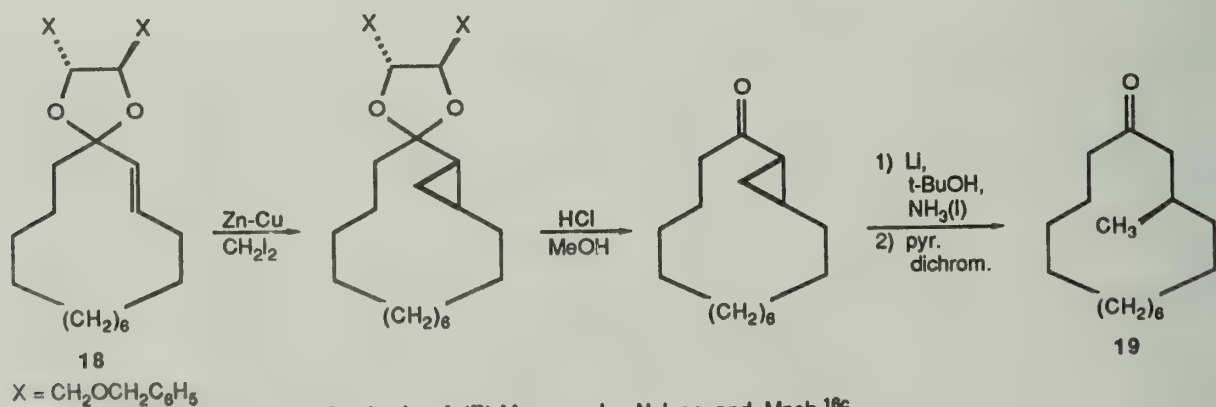
The  $\beta$ -hydroxy-sulfoximine directed Simmons-Smith reaction was used to synthesize the natural products (-)- and (+)-thujopsene (15)<sup>14a</sup> and (-)-rothrockene<sup>14b</sup> (16) in optical yields exceeding 90%. Figure 3 shows the reaction sequence for the synthesis of (-)-rothrockene.



Synthesis of (-)-rothrockene by Barburchyn, Johnson, and Glick.<sup>14b</sup>

Figure 3

A chiral acetal was utilized for an asymmetric synthesis of 17, in 90% ee.<sup>17</sup> The cyclopropyl derivative 17 is a key intermediate in the synthesis of 5,6-methanoleukotriene  $A_4$ , an inhibitor of leukotriene biosynthesis. Mash describe the enantioselective synthesis of (R)-muscone (19) from chiral ketal 18 (Fig. 4).<sup>16c</sup> The chemical yield over 7 steps was 60% and the optical purity was >95% ee.



Synthesis of (R)-Muscone by Nelson and Mash.<sup>16c</sup>

Figure 4



Optically active (1R,2S)-isocyanocyclopropanecarboxylate was obtained by alkylation of ethyl isocyanoacetate with optically active 1,2-dibromopropane and in the presence of sodium hydride.<sup>23</sup> The isocyanocyclopropane was then converted to the (1R,2S)-aminocyclopropanecarboxylate (80-90% optically pure) for use in a study of ethylene biosynthesis.

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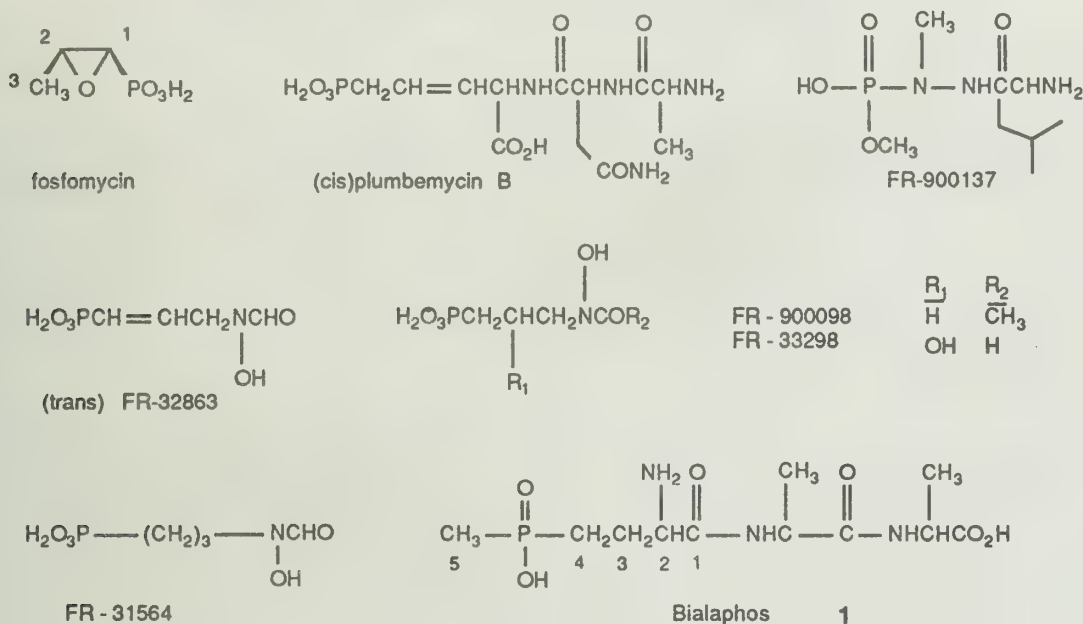
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## STRUCTURE AND BIOSYNTHESIS OF PHOSPHONIC ACID ANTIBIOTICS

Reported by Raymond Chung Man Lau

October 27, 1986

The phosphonic acid antibiotics comprise a small group of natural products isolated from *Streptomyces*.<sup>1,2c,3a-c</sup> They are generally colorless, and most are soluble in water and alcohols. The structures of these antibiotics (Fig. 1) have been determined by NMR and mass spectroscopy, and have been confirmed by synthesis.<sup>2a,b,3d-f,4</sup> Phosphonic acid antibiotics are inhibitors of cell wall biosynthesis, active against gram positive and/or gram negative bacteria; they are also relatively non-toxic.<sup>1a,2c,3a-d,5,6</sup>

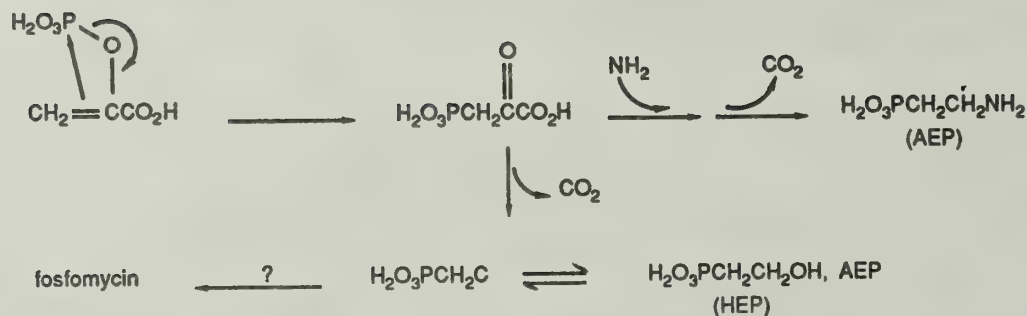


Structure of Phosphonic acid antibiotics

Figure 1

Studies on the biosynthesis of fosfomycin with labeled precursors showed that C-1 originates from C-1 or C-6 of glucose and C-3 originates from methionine.<sup>7</sup> Rogers et. al. proposed that the early stages in the biosynthesis of fosfomycin may be similar to pathway to aminoethylphosphonic acid (AEP) (Fig. 2) proposed by Warren.<sup>8-10</sup> Biotransformation studies with mutants further confirmed this hypothesis.<sup>11</sup>

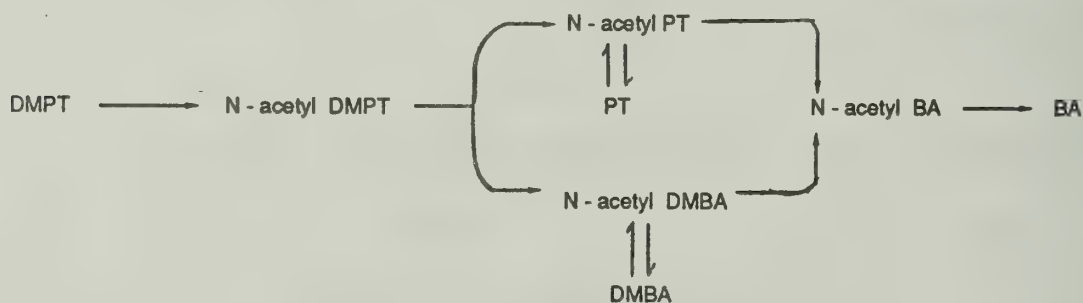
Bialaphos (BA) 1 is a herbicide that shows antifungal activity against plant pathogens.<sup>12</sup> Seto and coworkers studied the biosynthesis of BA through feeding of labeled precursors and mutant biotransformations.<sup>13</sup> They found that the C-1/C-2 and C-3/C-4 pairs are derived from different precursors and that the methyl group (C-5) comes from methionine. They proposed that PEP is an early precursor and the C-P bond is formed by an intramolecular rearrangement as it is in the biosynthesis of AEP and fosfomycin. Supplementation experiments with fluoroacetic acid (MFA), a strong inhibitor of aconitase, allowed Seto et. al.<sup>13g</sup> to propose part of the biosynthetic pathway as an analogue of the TCA



Proposed biosynthetic pathway to aminoethylphosphonic acid<sup>8</sup> and fosfomycin.<sup>7</sup>

Figure 2

cycle. Fermentation of new mutants with genetic blocks(s) after the formation of demethylphosphinothricin (DMPT) led to the discovery of N-acetylated metabolites in the broths. Biotransformation of these metabolites indicated that they are possible biosynthetic intermediates. Seto et al. then postulated the final steps of the biosynthesis of BA with N-acetylated derivatives as the advanced intermediates (Fig. 3).



Proposed final steps of bialaphos biosynthetics<sup>13a</sup>  
(PT - phosphinothricin, DMBA - demethylbialaphos)

Figure 3

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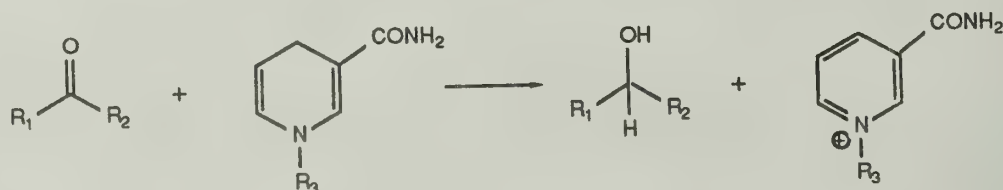
**THE CHEMISTRY OF 1,4-DIHYDRONICOTINAMIDE REDUCTIONS:  
ANALYSIS OF A MECHANISTIC CONTROVERSY**

Reported by Robert P. Lemieux

November 17, 1986

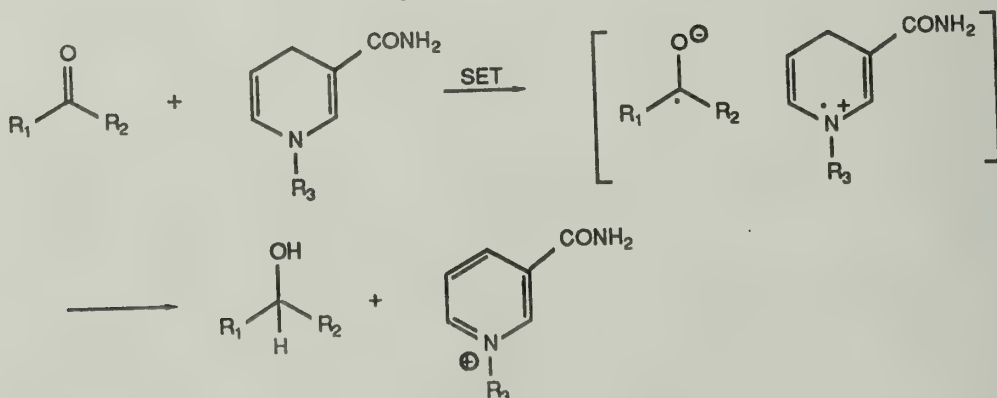
Determination of the mechanism for the reduction of carbonyl and related groups by N-alkyl-1,4-dihydronicotinamides has been a focus for a number of investigations since the 1950's.<sup>1</sup> In a pioneering study, Westheimer<sup>2</sup> proposed a one step hydride transfer mechanism for the reduction of thiobenzophenone by N-benzyl-1,4-dihydronicotinamide based on evidence obtained from solvent, substituent, and kinetic isotope effects.

Scheme I



The direct hydride transfer mechanism, as shown in Scheme I, was generally accepted until 1971 when Steffens and Chipman<sup>3</sup> reported the observation of a discrepancy between the kinetic isotope effect ( $k_H/k_D$ ) and the product isotope effect ( $Y_H/Y_D$ ) for the reduction of trifluoroacetophenone with N-alkyl-[4,4-<sup>1</sup>H<sub>2</sub>]- and [4-<sup>1</sup>H, 4-<sup>2</sup>H]-1,4-dihydronicotinamides in aqueous solution. These results were taken as evidence for a multistep mechanism in which an intermediate would occur on the reaction pathway. Further work by Creighton and Sigman<sup>4</sup> on the reduction of N-methylacridinium ion in aqueous and methanolic solution resulted in similar isotope effect discrepancies. In view of the reported propensity of 1,4-dihydronicotinamides to act as electron donors in the presence of certain oxidizing agents,<sup>5</sup> a mechanism involving an initial electron transfer followed by a hydrogen atom transfer, as shown in Scheme II, was proposed.

Scheme II

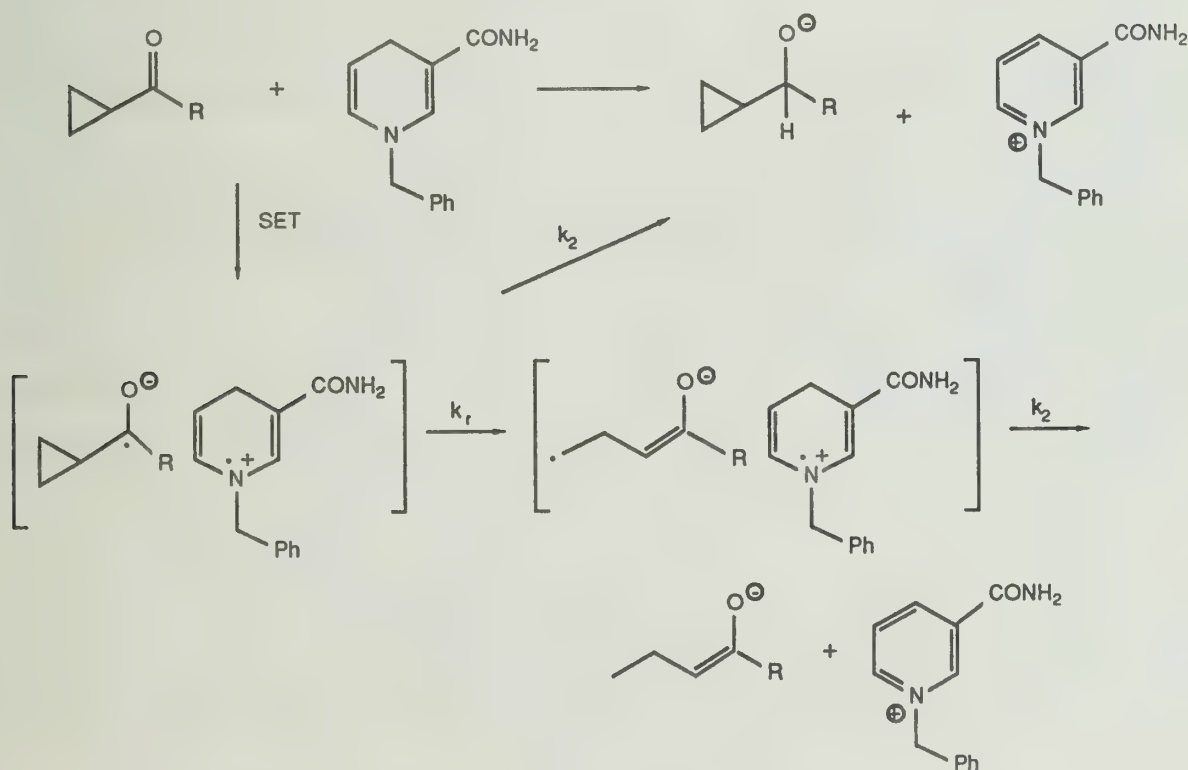


This mechanism was argued to be consistent with the isotope effect discrepancies, if the initial electron transfer is rate determining. Further investigation on the reduction of trifluoroacetophenone substrates revealed no significant isotope effect discrepancy when the reactions were run in the presence of Mg(II) or Zn(II) ions in an aprotic solvent.<sup>6-10</sup> These results were interpreted in favor of an electron transfer mechanism in which the hydrogen transfer step is rate determining.

This mechanism was later brought into question by van Eikeren and Chipman who found that, in the presence of water, a competing reversible formation of a bimolecular adducts could be responsible for the discrepancy between kinetic and product isotope effects.<sup>11,12</sup> In the meantime however, persistent claims for an electron transfer mechanism were made, based on the observation of isotope effect discrepancies in the reduction of N-methylacridinium ion in anhydrous acetonitrile by N-alkyl-1,4-dihydronicotinamides<sup>13,14</sup> and by the non hydratable 3-carbamoyl-N-benzyl-1,4-dihydroquinoline.<sup>15</sup> These claims however, were subsequently discredited in reports by Bruice<sup>16</sup> and Verhoven<sup>17</sup> who found that secondary isotope effects and isotope scrambling could account for the reported discrepancies.

More recently, support for a one step hydride transfer mechanism has been provided by investigations of the reduction of cyclopropyl ketones by N-benzyl-1,4-dihydronicotinamide.<sup>18,19</sup> Because the cyclopropylcarbinyl radical is known to undergo rapid unimolecular ring opening<sup>20</sup> with a rate constant of  $1.3 \times 10^8 \text{ sec}^{-1}$ , the use of these substrates may provide an opportunity to distinguish between a single electron transfer and hydride transfer mechanism by simple product analysis as shown in Scheme III.

Scheme III



Accordingly, it was shown that cyclopropane glyoxylic acid<sup>18</sup> and cyclopropyl 2-pyridylketone<sup>19</sup> undergo reduction with N-benzyl-1,4-dihydronicotinamide in acetonitrile to produce the corresponding alcohols without any detectable ring opening. These results were taken as strong evidence for a direct hydride transfer mechanism.

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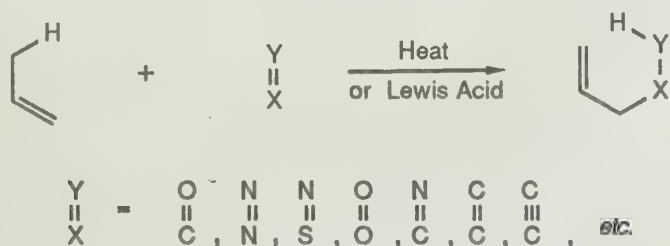
## RECENT INVESTIGATIONS ON ENE REACTION MECHANISMS

Reported by Zhiguo Song

November 24, 1986

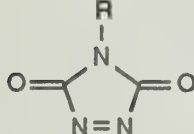
An ene reaction usually involves bond formation between an olefin with allylic hydrogens (the "ene") and a electron deficient double or triple bond (the "enophile") accompanied by double bond shift and hydrogen transfer, as shown in Scheme I. Ene reactions can occur under thermal or Lewis acid catalysis conditions with high regio- and stereoselectivities. They also offer an excellent means for carbon-carbon bond formation in synthesis and have been extensively exploited.<sup>1</sup>

Scheme I



In recent years, the mechanism and synthetic applications of ene reactions have drawn much attention and a group of enophiles, as listed in Table 1, have been vigorously investigated. The mechanisms proposed for the ene reactions range from a concerted pathway with a cyclic transition state<sup>2</sup> to a stepwise mechanism with the formation of the intermediate as rate determining step.<sup>3,4,6</sup> The intermediate can be a freely rotating open-chain zwitterion,<sup>9b</sup> or it can have a rigid three-membered ring structure.<sup>4,7</sup> The experimental evidence has come from regio- and stereochemistry of the ene reaction,<sup>2a,5a</sup> activation parameter determinations,<sup>5b,c,10b</sup> linear free energy relationships,<sup>5a</sup> and most importantly, kinetic isotope effects on the hydrogen transfer.

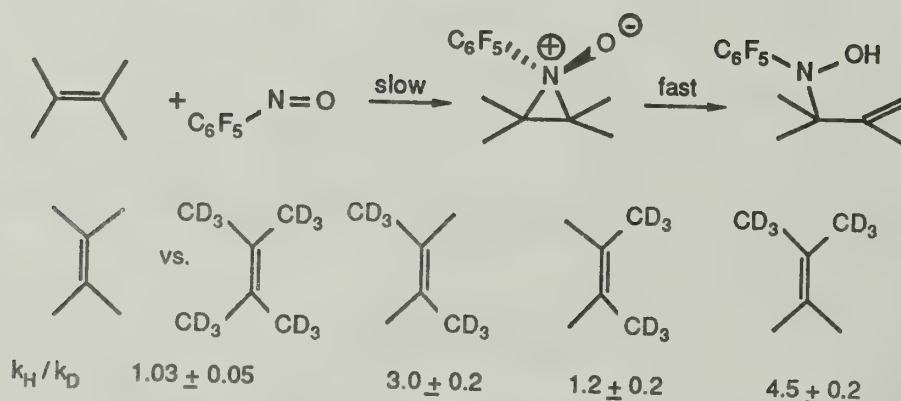
Table 1. Enophile Reagents and Catalysts (References)

$\text{MeO}_2\text{CN}=\text{NCO}_2\text{Me}$	(2)	$\text{C}_6\text{F}_5\text{-N=O}$	(7d)
$\text{CH}_3\text{C(=O)OAc} / \text{ZnCl}_2$	(3)	$\text{CH}_3\text{C}\equiv\text{O}^+\text{SbCl}_6^-$	(8a)
$\text{CH}_2=\text{O} / \text{AlMe}_2\text{Cl}$	(4)	$\text{HC}\equiv\text{CCO}_2\text{Me} / \text{AlEtCl}_2, \text{AlCl}_3$	(8b,4)
$(\text{RO}_2\text{C})_2\text{C=O}$	(5,6)	$\text{OS=N-Ts}$	(9)
	(7)	$\text{CCl}_3\text{CH=N-SO}_2\text{C}_4\text{F}_9$	(9b)
		$\text{O=O}^1$	(10)

Kinetic isotope effects not only can reveal if an ene reaction is concerted or stepwise,<sup>2,3,4</sup> but also can provide some insight into the detailed

structural features of the intermediates.<sup>4,6,7,9</sup> One example is given in Scheme II.<sup>7d</sup>

Scheme II



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**TUNICHLORIN A - A NOVEL NICKEL CHLORIN ISOLATED FROM A TRIDIDEMNUM  
SPECIES CARIBBEAN TUNICATE**

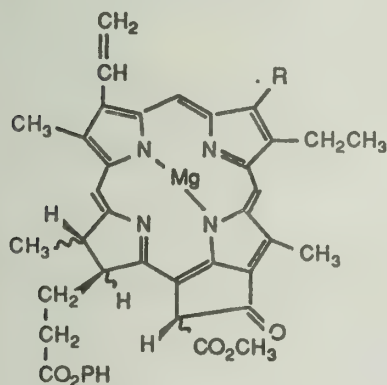
Reported by Keith C. Bible

December 4, 1986

The association of algae and marine tunicates has been known for over a century,<sup>1,2</sup> and has sometimes been utilized as a taxonomic marker for the classification of Didemnadae family tunicates (sea squirts).<sup>1</sup> A study undertaken to resolve taxonomic uncertainty of the alga associated with the Trididemnum species tunicate which produces didemnins (potent antineoplastic and immunoregulatory agents, one of which is now in clinical anti-cancer trials)<sup>3</sup> revealed the presence of a novel blue-green pigment (tunichlorin A).

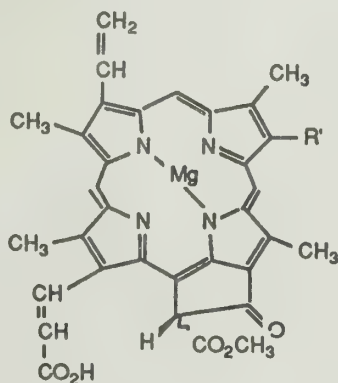
Tunichlorin A was isolated from chloroform tunicate extracts by repeated normal-phase (silica) and reverse-phase (C-18) HPLC. Although the underivatized pigment was too unstable to allow complete chemical characterization, a methanolysis product of the pigment was stable enough to be identified by spectroscopic and chemical methods. Absorption spectroscopy, low and high resolution fast atom bombardment mass spectrometry, proton and carbon NMR spectrometry (with homonuclear decoupling and n.o.e. studies), atomic absorption spectrometry and infrared spectrometry were utilized in the structure determination.

Tunichlorin A is quite distinct from other known marine chlorins and chlorophyll derivatives (e.g., chlorophylls a [1], b [2], c [3], d [4]; and 13,<sup>2</sup> 17-<sup>3</sup>cyclopheophorbide enol [5]).<sup>2,4-8</sup>



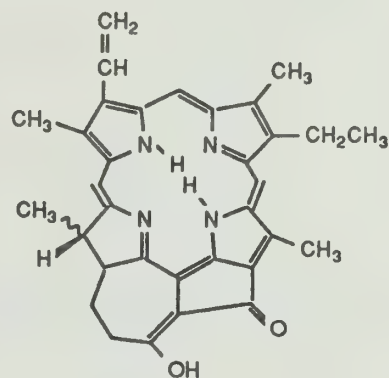
1: R = CH<sub>3</sub>;

2: R = CHO; PH = C<sub>20</sub>H<sub>38</sub>



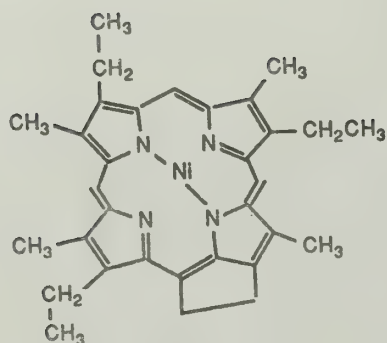
3: R' = C<sub>2</sub>H<sub>5</sub>;

4: R' = CH=CH<sub>2</sub>

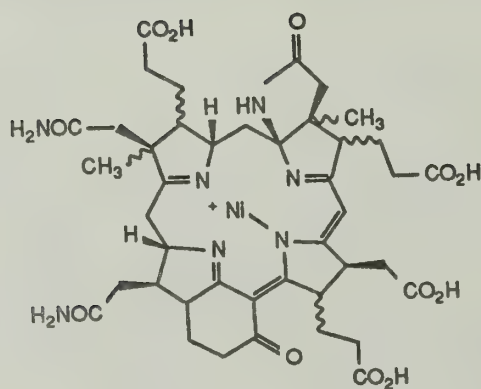


5

Although nickel porphynoids (e.g., 6) are often found in crude petroleum reserves,<sup>9,10</sup> only one other such compound (Factor F430, 7) has yet been isolated from a living organism.<sup>11</sup>



6



7

F430, a cofactor involved in the conversion of  $C_1$  compounds to methane in methanogenic bacteria, however, is a highly reduced porphyrinoid quite dissimilar to tunichlorin A.<sup>11</sup> The biosynthesis and metabolic significance of tunichlorin A have yet to be determined, but the compound may represent a tunicate catabolite of an algal chlorophyll.

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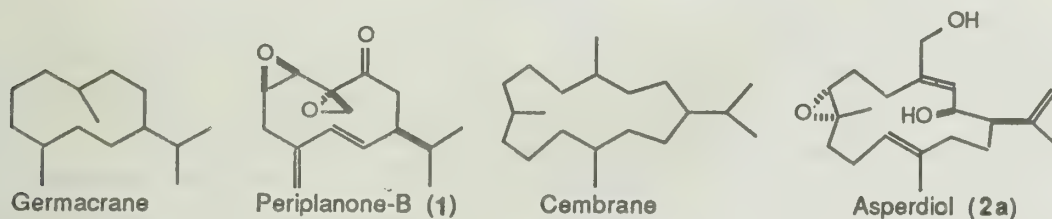
## MACROCYCLIZATION METHODS USED IN GERMACRANE AND CEMBRANE NATURAL PRODUCTS

Reported by Young Choon Moon

December 8, 1986

## INTRODUCTION

Germanacranes comprise a large class of 10-membered monocyclic sesquiterpenes some of which are believed to serve as biogenetic precursors of other bicyclic and tricyclic sesquiterpenes.<sup>1</sup> Many of the germacranolides exhibit biological activities as pheromones, antibiotics, and cytotoxins. For example, periplanone B (1)<sup>2</sup> is an extraordinarily potent sex attractant of the American cockroach (Scheme I). Cembranes are unique 14-membered ring

Scheme I

diterpenes which have been isolated mainly from marine sources.<sup>3</sup> Asperdiol (2a)<sup>4</sup> is a cembrane possessing antibiotic and antitumor activity (Scheme I). The intense interest in the development of methods<sup>5</sup> for the synthesis of these medium- and large-ring carbocycles stems from their biological activities as well as their unusual ring structures. The numerous approaches used to form the germacrane and cembrane rings may be grouped into the three following categories: (1) acyclic ring closure, (2) ring cleavage, and (3) ring expansion and ring contraction.

## MACROCYCLIZATION METHODS

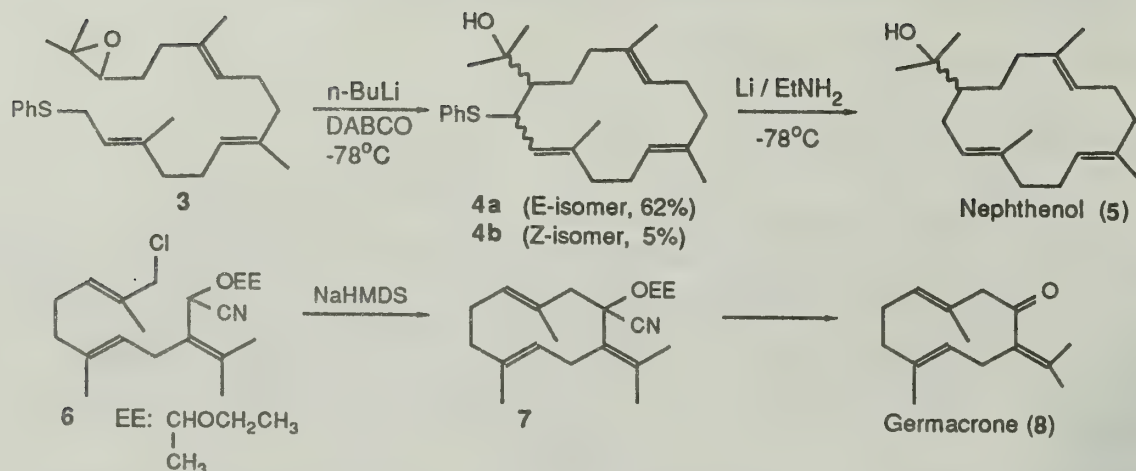
**Acyclic Ring Closure**

Direct ring closure has been the most extensively used of the three different methods, despite potential difficulties arising from strain and entropy effects.

**Alkylation**

Itô<sup>6</sup> has studied the cyclization of sulfur-stabilized anions<sup>9a</sup> derived from suitably functionalized acyclic terpenoids (Scheme II). Nephthenol precursor 4a was formed by a Biellmann-type cyclization<sup>6a</sup> of epoxide 3 in 62% yield along with a small amount (5%) of geometric isomer 4b. (±)-Cembrene A,<sup>4a</sup> (±)-nephthenol (5),<sup>6a</sup> (±)-3Z-cembrene A (46),<sup>6b</sup> (±)-cembrenene,<sup>6b</sup> and (±)-cembra-3E,7E,11E,15(17)-tetraen-trans-16,2-olide<sup>6c</sup> have been synthesized via the crucial intermediates 4a and 4b. (±)-Hedycaryols (22)<sup>6d,e</sup> have also been synthesized in a similar manner by cyclization of 10,11-epoxyfarnesyl

## Scheme II



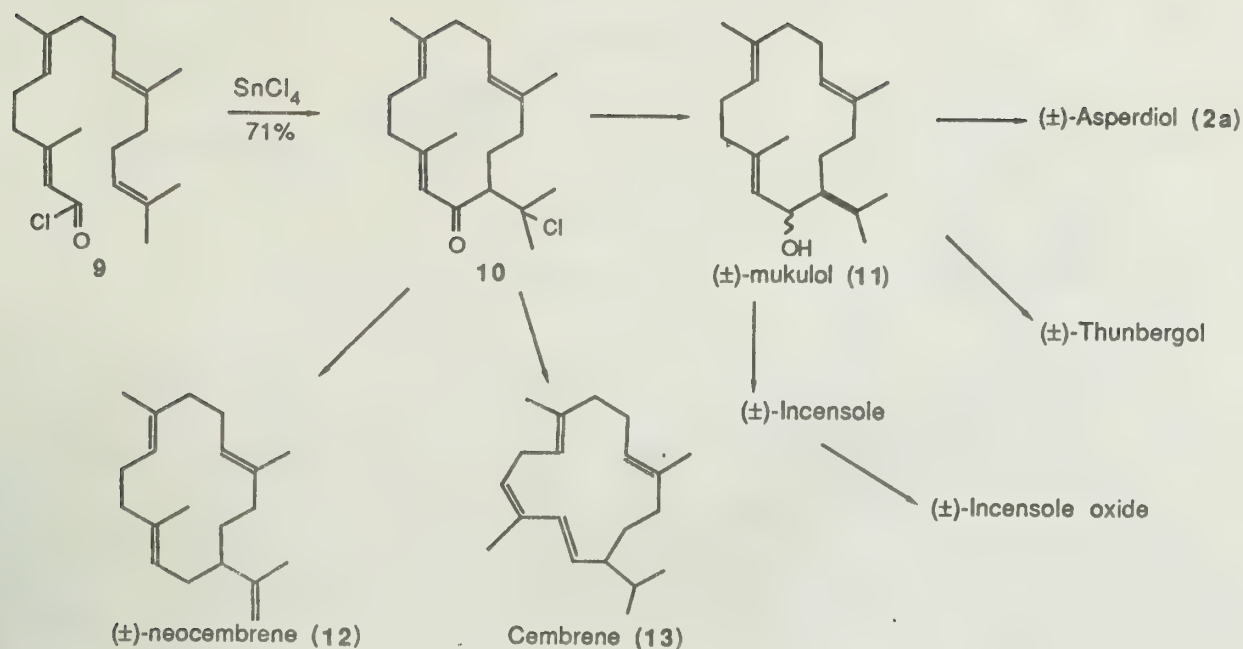
phenyl sulfide and desulfurization of the allylic sulfide. Although this method has been used effectively in syntheses of the cembranes<sup>6a,b,c</sup> and germacrane<sup>6c,d</sup> cited above, the formation of double bond isomers during the cyclization or desulfurization reactions has been a problem.

The protected cyanohydrin method has been introduced by Takahashi.<sup>7</sup> The carbanion derived from the protected cyanohydrin acts as an acyl anion equivalent and alkylation occurs without any isomerization of the double bonds. The cyclization of protected cyanohydrin **6** was performed using sodium hexamethyldisilazide (NaHMDS) as base. Germacrone (**8**)<sup>7a</sup> was obtained in 84% yield after hydrolysis of the cyclized product **7**. (+)-Acoragermacrone<sup>7b</sup> and (+)-mukulol (**11**)<sup>7b</sup> have been also synthesized by this method. Activation of the methine proton by a nitrile and phenylthio group has been employed by Kitahara<sup>8</sup> in syntheses of (-)-dihydrogermacrene D<sup>8a</sup> and (-)-periplanone B.<sup>8b</sup> The Kitahara method utilizes a modified Takahashi synthon in which the  $\alpha$ -phenylthio nitrile serves as a masked terminal methylene double bond equivalent. Allyl sulfide<sup>9a</sup> and alkyl sulfones<sup>9b,c</sup> have been used as stabilizing groups in carbanionic cyclizations.

## Friedel-Crafts Cyclization of Olefins

Biogenetic-type cationic cyclization of a geranylgeraniol equivalent has been accomplished by Kato<sup>10</sup> (Scheme III). Geranylgeranic acid chloride (**9**) underwent cyclization in the presence of tin tetrachloride as a catalyst to afford  $\beta$ -chloro ketone **10**. This 14-membered ring ketone **10** was used as a key intermediate in syntheses of (+)-mukulol,<sup>10a</sup> (+)-cembrene (**13**),<sup>10b</sup> (+)-neocembrene (**12**),<sup>10c</sup> (+)-incensole,<sup>10d,f</sup> thunbergol,<sup>10e</sup> (+)-asperdiol,<sup>10i</sup> and incensole oxide.<sup>10f</sup> (E,E,E)-, (E,Z,E)-, and (E,E,Z)-geranylgeranic acid chlorides gave only 14-membered chloro ketones after cyclization. These results imply that the 10,11-double bond is resistant to attack by the acid chloride presumably owing to the strain of the 10-membered rings. However, a 6-membered  $\beta$ -chloro ketone was the predominant product from cyclization of the 2Z-isomer.<sup>10h</sup>

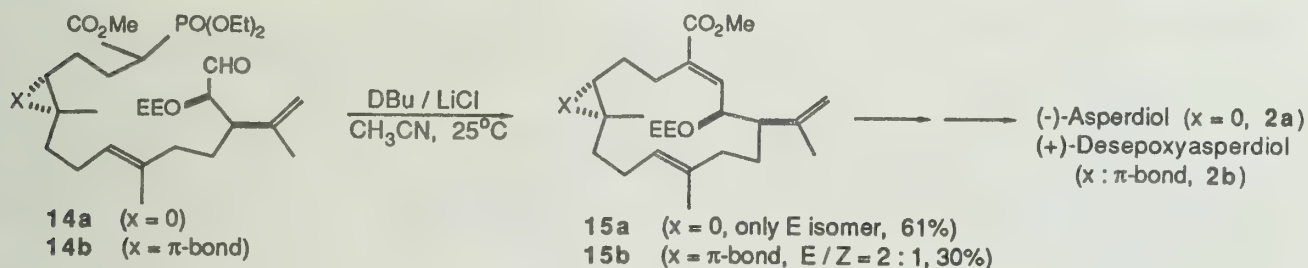
### Scheme III



### Horner-Emmons Olefination

The Horner-Emmons reaction was used effectively in the synthesis of (-)-asperdiol and (+)-desepoxyasperdiol (**2b**) by Tius<sup>11</sup> (Scheme IV).

### Scheme IV



Phosphonate aldehyde **14a** was converted to the asperdiol precursor **15a** as a single E-isomer (61% yield) under the Masamune-Rousch reaction conditions.<sup>11</sup> The complete absence of the Z-isomer was unexpected because the olefination of desepoxy **14b** gave a 2:1 mixture of E- and Z-isomers **15b**.

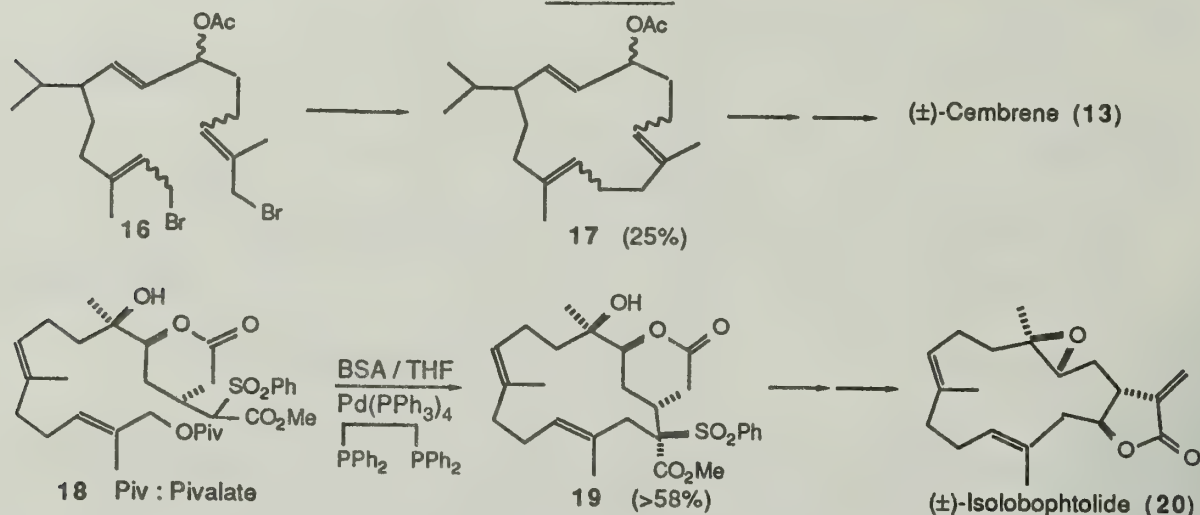
### Organometallic Coupling Reactions

In the synthesis of (±)-cembrene (**13**), Dauben<sup>12</sup> applied the nickel tetracarbonyl coupling of terminal allyl bromides **16** as a key step (Scheme V) to form the 14-membered ring. The coupling reaction was accomplished by treating dibromide **16** with nickel carbonyl in N-methylpyrrolidone. A mixture of isomeric trienes **17** was obtained in 25% yield. Although the nickel carbonyl coupling reaction is compatible with isolated double bonds or esters, other more reactive functional groups such as ketones or aldehydes react with the nickel reagent.



Marshall<sup>13</sup> has employed the  $\pi$ -allyl palladium methodology in a reagent synthesis of ( $\pm$ )-isolobophytolide intermediate 19 (Scheme V). Cyclization of

**Scheme V**



the sulfonyl ester pivalate 18 occurred smoothly upon slow addition of the enol silane derivative to the palladium(0) catalyst in the presence of diphos at moderately dilute concentration. In Still's synthesis of ( $\pm$ )-asperdiol (2a),<sup>12</sup> the macrocycle was formed by intramolecular addition of an allyl chromium reagent to an aldehyde. This threo-selective reaction afforded two diastereomeric homoallylic alcohols in a 4:1 ratio (64% yield).

Wittig type reaction and organometallic reagents have not been used in germacrane syntheses.

### Ring Cleavage

Bicyclic or polycyclic compounds can be converted to monocyclic structures by cleavage of intraannular bonds. This strategy has been realized by boronate fragmentation, cyclohexadiene photolysis, and formal olefin metathesis.

### Boronate Fragmentation

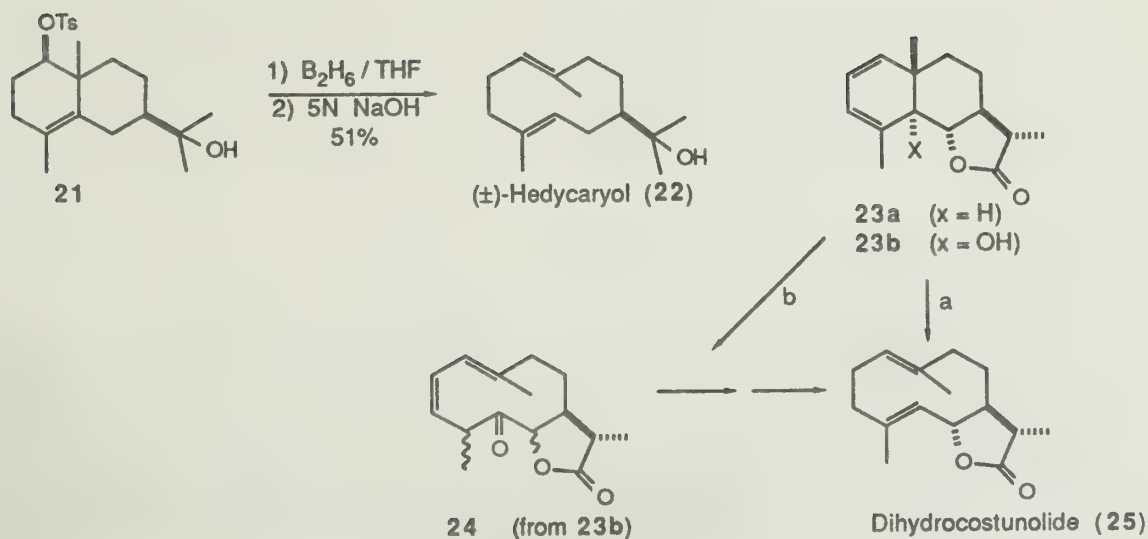
Wharton<sup>15</sup> has synthesized ( $\pm$ )-hedycaryol (22) using Marshall's boronate fragmentation method. Octalyl tosylate 21 was hydroborated with diborane at room temperature and the resulting organoborane was treated with base at 65°C for 13 hours to afford ( $\pm$ )-hedycaryol 22 in 51% yield.

### Photolysis of Cyclohexadienes

The cleavage of hexahydronaphthalene derivatives to 10-membered rings may be accomplished photochemically. Dihydrocostunolide (25) has been prepared by this method<sup>16</sup> (Scheme VI). The presence of the hydroxyl group in 23b is crucial to the success of this transformation because tautomerization of the initially produced enol to the ketone 24 provides the driving force to form the 10-membered ring. In the first synthesis of dihydrocostunolide by Corey,<sup>16a</sup>



## Scheme VI

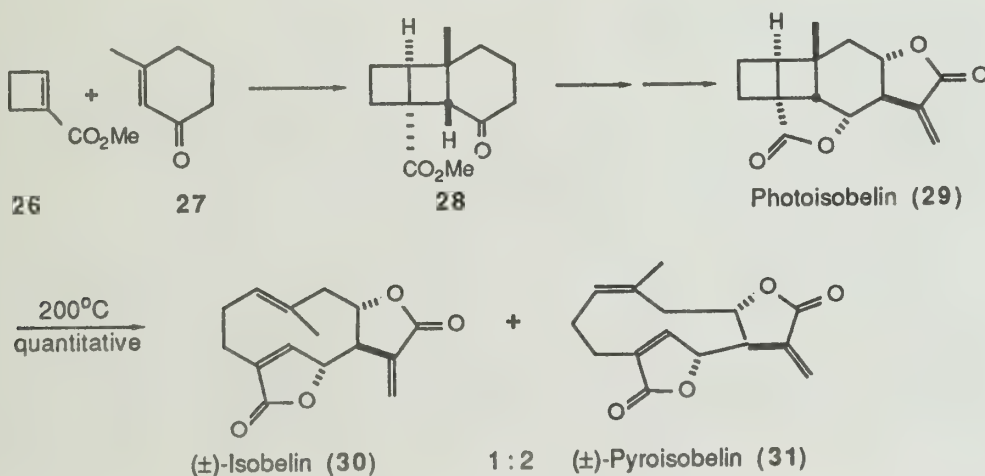


irradiation of 23a which lacks the hydroxyl group afforded dihydrocostunolide in only 10% yield. In contrast photo-isomerization of the hydroxyl-bearing 23b gave dienone 24 in ca. 80% yield.<sup>16c</sup>

## Metathetical Cycloaddition and Retrocycloaddition

Thermal cleavage of strained tricyclic compounds containing cyclobutane rings provides another route to macrocyclic compounds. This approach was independently introduced by Lange<sup>17</sup> and Wender.<sup>18</sup> Tricyclo[4.4.0.0<sup>2,5</sup>]decane derivative 28 obtained via photochemical [2+2]-cycloaddition of cyclobutene 26 and enone 27 was transformed to fully functionalized photoisobelin (29) in a sealed tube gave  $(\pm)$ -isabelin (30) and  $(\pm)$ -pyroisobelin (31) in a 1:2 ratio in quantitative yield (Scheme VII).

## Scheme VII



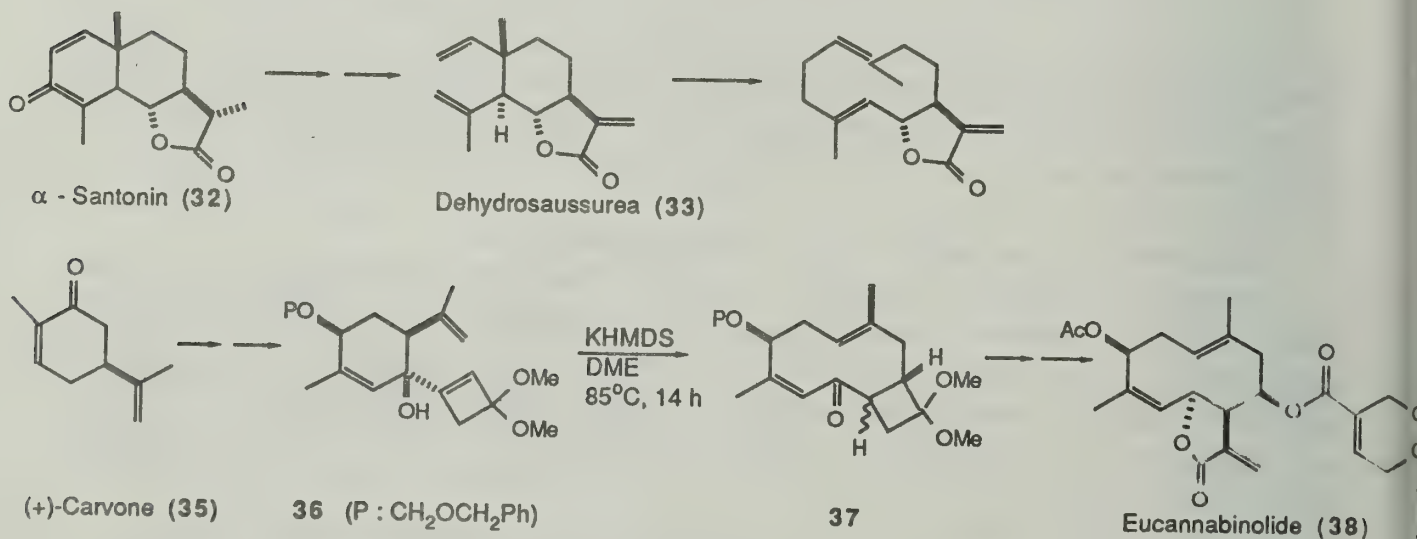
( $\pm$ )-Hedycaryol (22),<sup>15</sup> dihydrocostunolide,<sup>16</sup> and ( $\pm$ )-isobelin (30)<sup>18</sup> have been synthesized by ring cleavage methods. Notably, the interconversion between isobelin (30) and photoisobelin (29) under photochemical and thermal conditions is an elegant application of well-known electrocyclic reactions. Ring cleavage methods have not been used to synthesize cembrenes presumably because the required precursors, which would contain a fused 6,10-membered ring or tricyclo[8.4.0.0]butadecane ring system, would be difficult to prepare.

## RING EXPANSION/RING CONTRACTION METHODS

### Cope Rearrangement

The well-known Cope rearrangement has been applied to the synthesis of (+)-costunolide (34) and ( $\pm$ )-linderlactones by Grieco<sup>19a</sup> and Magnus<sup>19b,c</sup> respectively. Dehydrosaussurea (33), prepared from santonin (32) in 12 steps, was converted to (+)-costunolide via [3,3]-sigmatropic rearrangement in 20% yield along with a 42% yield of recovered reactant 33 (Scheme VIII).

Scheme VIII



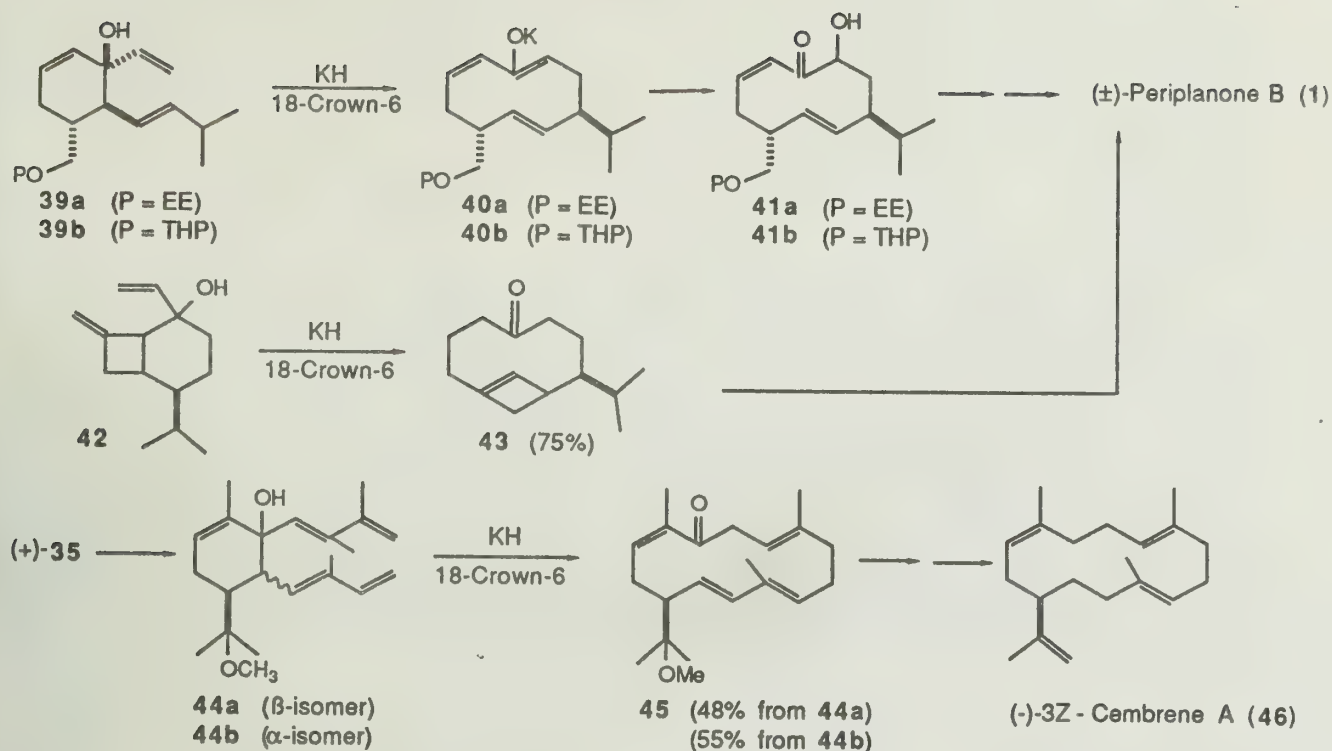
### Oxy-Cope Rearrangement

The anion-induced oxy-Cope rearrangement, first observed by Evans, has been used to form macrocyclic ketones by ring-expansion.<sup>20,21,22</sup> Divinyl carbinol 39, readily prepared from (+)-carvone (35), was rearranged to 37 by reaction with potassium hexamethyldisilazide (KHMDS). Dienone 37 gave eucannabinolide (38) after several chemical operations.<sup>20b</sup>

Periplanone B (1) has been synthesized by four different groups<sup>8b,21</sup> three of which used anionic oxy-Cope rearrangements to form the germacrone skeleton (Scheme IX).

Recently, Wender<sup>22</sup> has developed an oxy-Cope type [5,5]-sigmatropic rearrangement for the synthesis of (-)-(3Z)-cembrene A (46) (Scheme IX). The

## Scheme IX

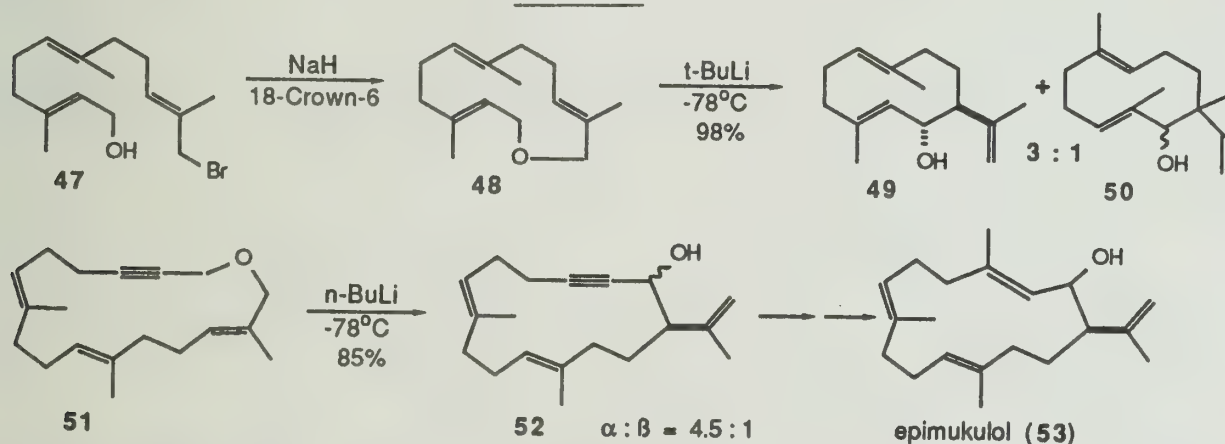


dibutadienyl-cyclohexanols, **44a** and **44b**, prepared from (+)-carvone (**35**) underwent [5,5]-rearrangement upon reaction with potassium hydride (KH) and 18-crown-6 ether to afford ketone **45**.

## [2,3]-Wittig Rearrangement

Takahashi<sup>23a</sup> and Marshall<sup>23b</sup> applied [2,3]-sigmatropic rearrangements to the synthesis of 10- and 14-membered ring compounds, respectively (Scheme X).

## Scheme X



Takahashi showed that the rearrangement is highly stereoselective (>98%) although deprotonation occurred with moderate regioselectivity (3:1). In contrast, the 17-membered cyclic ether **51** rearranged to the 14-membered carbocyclic alcohol **52** with high regioselectivity (ca. 100%) and moderate stereoselectivity (4.5:1).

Ring expansion and contraction via sigmatropic rearrangements are usually stereoselective. Alkoxide-induced oxy-Cope rearrangements have been used to advantage in the synthesis of germacranes and cembranes. The [2,3]-Wittig reaction offers another highly selective approach to these macrocyclic terpenes.

## SUMMARY

In the germacranes area, nine different methods have been successfully applied to the synthesis of fifteen different natural products. Acyclic ring closure, ring cleavage, and ring expansion/contraction approaches have been extensively used. The latter two approaches usually afford better opportunities for stereocontrol and accommodation of functionality as a result of using cyclohexane or decalin precursors. Wittig type olefination and Friedel-Crafts acylation reactions have not been applied to these moderately strained 10-membered rings. Six methods have been used for the synthesis of ten different cembrane diterpenes using acyclic ring closure methods in most cases.

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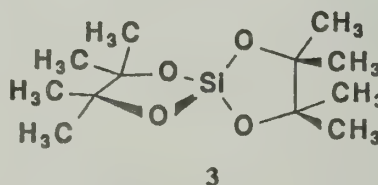
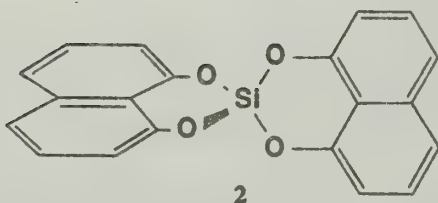
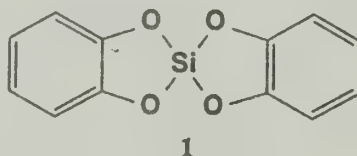
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# THE EFFECTS OF LIGANDS ON THE GROUND STATE GEOMETRY OF TETRACOORDINATE SILICON

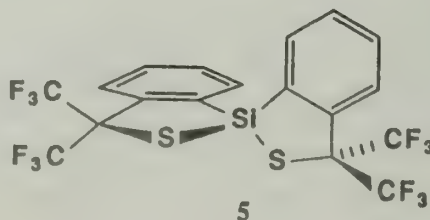
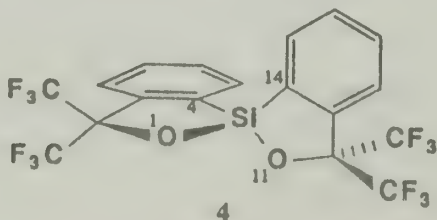
Reported by Craig C. Henderson

April 17, 1986

The first claim<sup>1</sup> of planar tetracoordinate silicon appeared in the literature when Meyer and Nagorsen concluded from a crystallographic symmetry argument that the catechol derivative **1** must be planar at the silicon center, at least in the solid state. Reinterpretation<sup>2</sup> of the data by Dunitz showed that the experimental evidence for planar silicon offered by Meyer and Nagorsen was insufficient to establish silane **1** as the first example of planar tetracoordinate silicon. Nevertheless, this report led to a considerable amount of research directed towards the isolation of a planar silicon species. Several X-ray crystal structures of tetraoxysilanes (**2**<sup>3</sup>, **3**<sup>4</sup>) have been reported recently, but the results of these studies showed only slight deviations toward planarity at silicon.



A much larger distortion toward planarity at silicon was reported by Martin and Stevenson for silane **4**.<sup>5</sup> The X-ray crystal structure of **4** showed that the ground state geometry is a strongly distorted tetrahedron, with the dihedral angle between the planes formed by <sup>10</sup>O, <sup>14</sup>C, Si and <sup>11</sup>O, <sup>14</sup>C, Si being 96.1°, compared to the ideal angle of 90° for a tetrahedral geometry. Since silane **4** is so significantly distorted toward a trans-coplanar geometry, Martin and Stevenson proposed that the energy barrier ( $\Delta E$ ) for an inversion of **4** through a planar transition state might be low enough to measure experimentally. Initial evidence from magnetization transfer experiments in the <sup>19</sup>F NMR spectrum of **4** supported this conclusion, although an accurate value for  $\Delta E$  was not obtained from these experiments.



Quantum mechanical calculations<sup>6</sup> on  $\text{SiH}_4$  indicate that replacement of the hydrogens by  $\sigma$ -accepting and  $\pi$ -donating ligands will lower the energy of planar silicon relative to tetrahedral silicon. Martin and Stevenson concluded, therefore, that the large distortion of  $6.1^\circ$  observed for silane **4** is due to the ability of the bidentate ligands ( $\sigma$ -acceptors,  $\pi$ -donors) to stabilize the planar geometry relative to a tetrahedral arrangement. A narrow bond angle at silicon ( $94.3^\circ$ ), endocyclic to the strained five-membered ring, should also raise the energy of the tetrahedral arrangement (ideal angles  $109.28^\circ$ ) relative to the planar geometry (ideal angles  $90^\circ$ ).

Presumably both the electronic and the geometric features of the bidentate ligand in silane **4** contribute to the observed ground-state distortion, although the relative importance of each factor is not yet clear. The effect of changes in the electronic and geometric features of the ligand system in **4** on the ground-state geometry of the corresponding silane will be discussed in this seminar, as well as the synthetic schemes needed to produce these closely related silanes, such as silane **5**. Experimental methods for accurately measuring the energy difference ( $\Delta E$ ) between the distorted tetrahedral ground state and the higher energy planar state of **4** will also be presented and discussed.

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ORGANIC SEMINARS ABSTRACTS

1986-87, SEMESTER II

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# PHOTOLYSIS OF BRIDGEHEAD AZIDES: THE FORMATION OF ANTI-BRETT IMINES

Reported by Michael Kropp

February 5, 1987

Brett, in 1924, realized that double bonds tend to avoid ring junctions.<sup>1</sup> Brett's rule states that a double bond cannot be placed at the bridgehead of a bicyclic system which contains at least one atom in every bridge. Many studies have been done to examine the extent to which this rule is followed for bridgehead olefins.<sup>2</sup> Wiseman has predicted that if the trans double bond is contained in a cyclooctene or larger ring system of a bicyclo compound, it could be stable.<sup>2c</sup> More recently, bridgehead imines have received increasing attention, and certain strained anti-Brett bridgehead imines have been prepared, mainly via photolysis of bridgehead azides. This report will give an overview of the work that has been done on this subject.

## BACKGROUND

Before discussing bridgehead azides and imines specifically, it is helpful to review some basic aspects of alkyl azide photochemistry.<sup>3</sup> The photolysis of alkyl azides can follow several pathways (Fig. 1). The photolysis products arise either directly from the singlet azide or through a singlet nitrene. Through intersystem crossing or sensitized photolysis, products from the triplet manifold can arise in a similar fashion. In almost all cases, the direct photolysis of alkyl azides produces imines; as examples, methyl, ethyl, and t-butyl azides give the imines shown upon photolysis in a matrix (Eqs. 1-3). Although no products characteristic of a nitrene intermediate (i.e., those arising from insertion into C-H bonds) have been observed when these reactions are done in solution, it is still uncertain whether the imine comes directly from the excited azide, or from a nitrene intermediate.

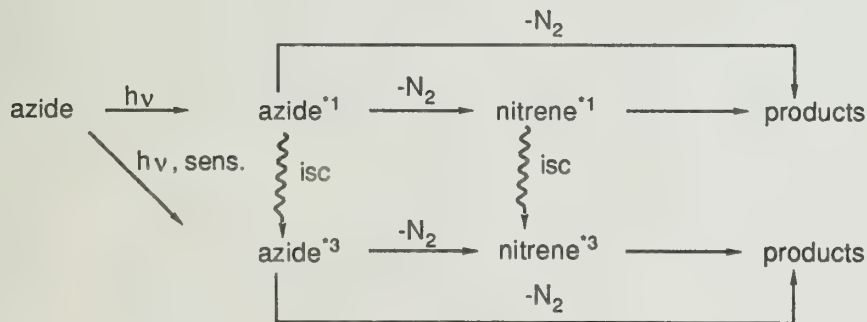
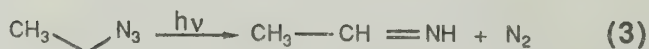
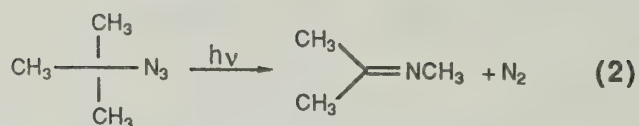
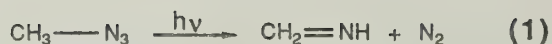


Figure 1



Kyba and Abramovitch have proposed that the imines arise via a concerted migration and loss of  $\text{N}_2$  from the excited azide.<sup>4</sup> They suggest that the migratory ratios observed when there is a choice of migrating substituents can be predicted from the ground state or excited azide conformations; it is not possible to make such estimates from a cylindrically-symmetrical nitrene intermediate. It should be noted that the authors found cases which gave different ratios than those predicted by their method, lending some doubt to the usefulness of this model.

There is, however, evidence to support nitrene intermediates, too. The observed migratory selectivities have been low, which has been viewed as evidence for a highly reactive nitrene intermediate. ESR signals have been observed in alkyl azide photolysis at 4K, indicative of a triplet nitrene.<sup>3a</sup> However, sensitized irradiation does not give imines, so the imines do not arise from the triplet manifold. Still, existence of a triplet nitrene has been interpreted as evidence for the operation of a stepwise formation of imines via singlet nitrenes. It is important, however, to realize that the observation of triplet nitrenes is completely consistent with a branched reaction pathway, with imine being formed by a concerted rearrangement and the triplet nitrene arising by intersystem crossing from the singlet azide. Thus, the observation of a triplet nitrene provides no evidence to distinguish between a concerted or stepwise formation of the imines.

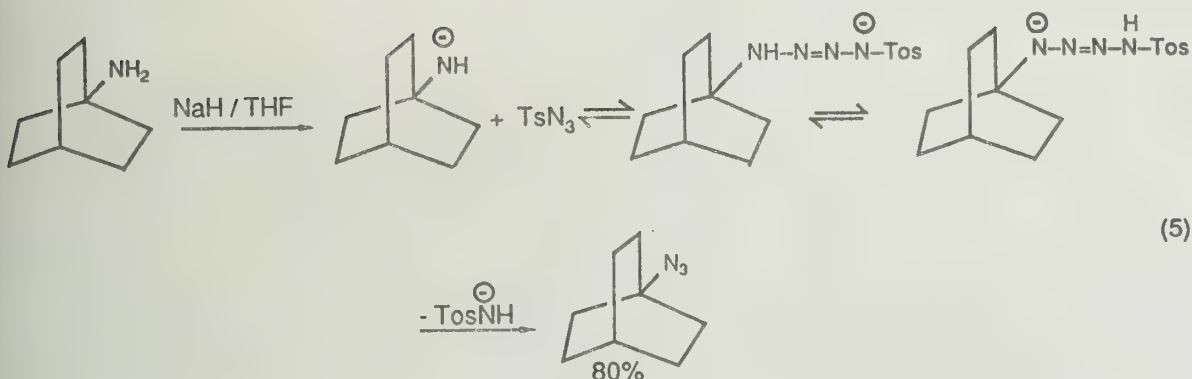
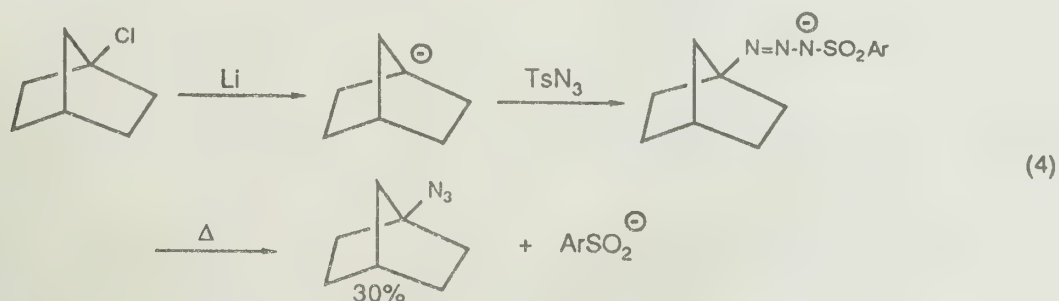
The best evidence to date supporting a concerted imine formation is from trapping experiments. Although nitrene products (e.g., C-H bond insertion) have been observed upon thermolysis of alkyl azides, attempts to trap a singlet nitrene upon photolysis have failed.<sup>3a</sup> There are only two examples of direct photolysis of azides leading to products generally accepted as those due to nitrene intermediates, and these studies have been questioned.<sup>3a</sup> This cannot be viewed as conclusive evidence against a nitrene, however, since the singlet nitrene would be a high energy, highly reactive species, and intramolecular rearrangement might proceed much faster than would typical intermolecular trapping reactions of the nitrene.

Thus, at present the results from photochemical studies of alkyl azides, though perhaps favoring a concerted process, are inconclusive. It may be that nitrenes are involved in some cases, but not others. It should also be noted that thermolysis and acidolysis of alkyl azides also give imines, as well as nitrene-type products. The mechanism of these decompositions is also in question, but probably is different from photolysis.



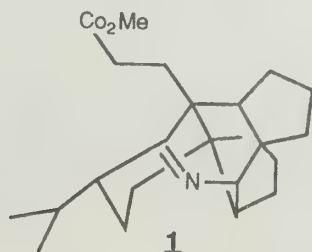
## SYNTHESIS OF BRIDGEHEAD AZIDES

The synthesis of bridgehead azides is illustrated by the methods used by Reed<sup>5</sup> and Sasaki<sup>6</sup> for the synthesis of 1-azidonorbornane and 1-azidobicyclo[2.2.2]octane, respectively (Eqns. 4 and 5).

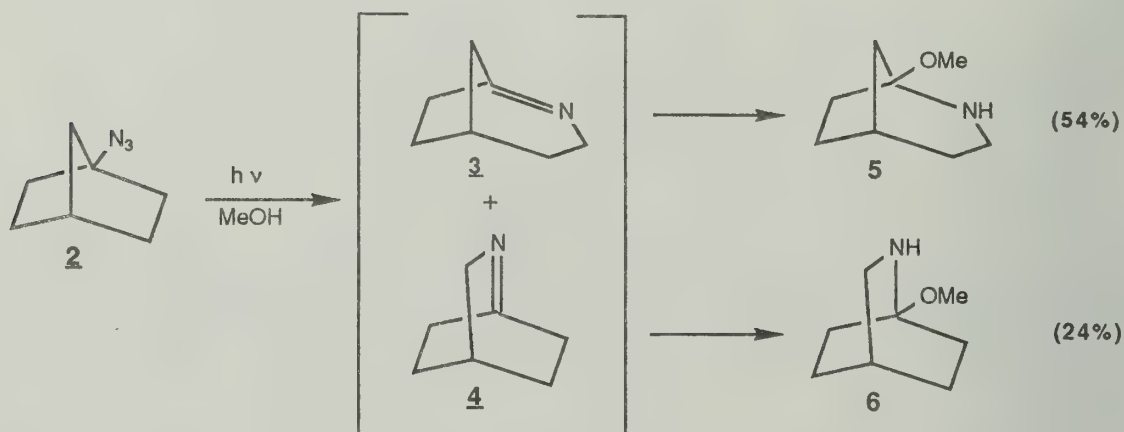


## SOLUTION CHEMISTRY

Prior to 1983, the only bridgehead imine which had been isolated was the 2-azabicyclo[3.3.1]non-1-ene system (1), as formed by treating the alkaloid methyl homosecodaphniphyllate with lead tetra-acetate.<sup>7</sup> The stability of this imine, in which the trans double bond is in an azacyclooctene ring, suggests that Wiseman's rule<sup>2c</sup> for olefins also holds for imines. The compound has an IR band at  $1600\text{ cm}^{-1}$ . This is at a lower frequency than typical  $\nu(\text{C}=\text{N})$  vibrations ( $\sim 1650\text{ cm}^{-1}$ ), indicating some strain on the  $\text{C}=\text{N}$  bond.

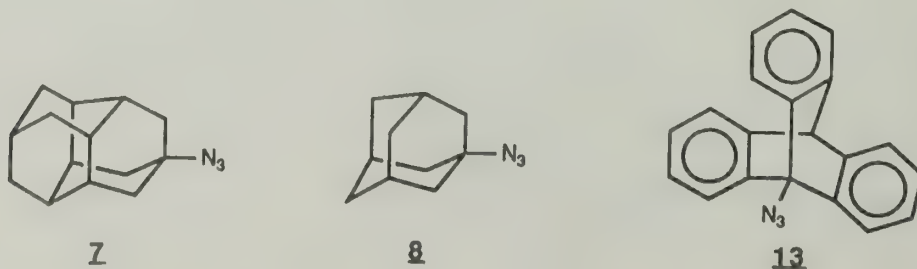


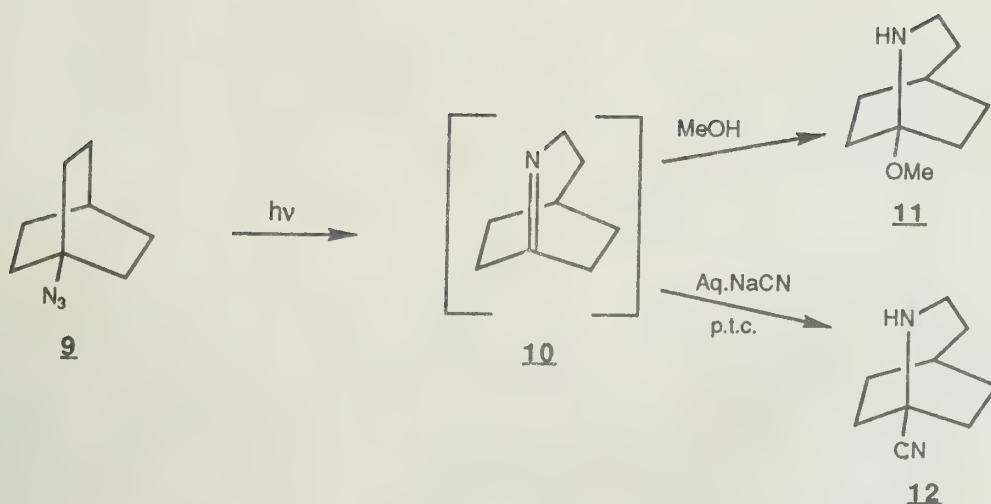
In 1971, Reed and Lwowski studied the photochemistry of 1-azidonorbornane (2).<sup>5</sup> Since the imines formed (3 and 4) would be anti-Bredt with nearly orthogonal p-orbitals, the authors expected that the rearrangement of 2 to 3 and 4 would be slow, and hoped that 2 would instead form nitrenes, which would undergo intermolecular nitrene chemistry. However, instead of giving nitrene type reactions, photolysis of azide 2 in methanol or propanol gave the alkoxy amines 5 (54%) and 6 (24%). Polymers were formed in inert solvents. Since the product ratios in this case are close to statistical, the authors argued against a C=N intermediate; they felt that the difference in strain in the two imines would have led to a non-statistical ratio of



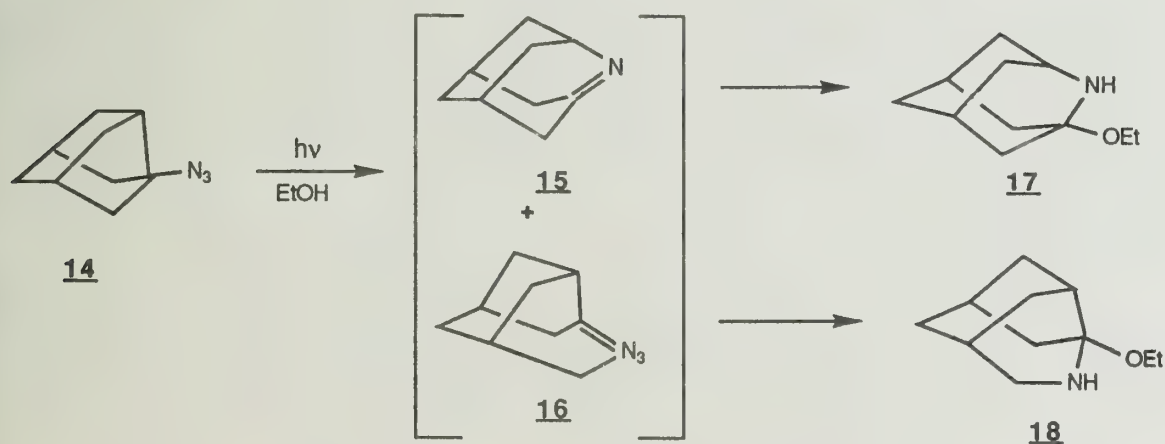
adducts. So instead, they proposed a concerted migration and alcohol addition. This argument against imines as intermediates, however, does not consider the possibility of an early transition state: if little or none of the strain difference between the two imines is actually felt in the transition state, they may be produced in a statistical ratio.

For symmetrical azides, the selectivity in product formation is not a factor. Sasaki has studied 4-azidodiamantane (7)<sup>11</sup>, while Sasaki and Quast have studied 1-azidoadamantane (8)<sup>12,13</sup> and 1-azidobicyclo[2.2.2]octane (9).<sup>6,14</sup> Quast has also studied 9-azidotriptycene (13).<sup>15</sup> In each case, methoxyamines were formed upon photolysis in MeOH, providing evidence for the imine as an intermediate. Sasaki also trapped the imines as the aminonitriles, by photolysing the azide in the presence of aqueous NaCN and a phase transfer catalyst. In inert solvents, polymers or dimers formed.

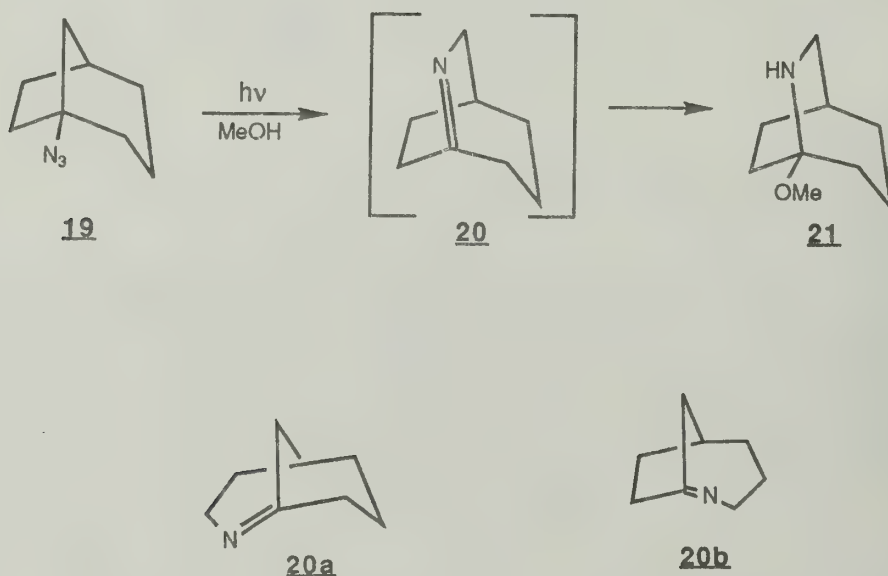




For unsymmetrical bridgehead azides, there is a choice as to which bond migrates. In many cases statistical migrations were observed, but there are also examples of nonstatistical selectivity. An example is the azide 3-azidonoradamantane (**14**), studied by Jawdosiuk and Kovacic.<sup>8</sup> When the azide was photolyzed in ethanol, the two ethoxyamines **17** and **18** were formed in a 1:1.10 ratio. Since the product distribution in this case was non-statistical, the adducts were proposed to arise from the corresponding imines, and the product ratio was explained by Kyba and Abramovitch's model of ground state conformation control.<sup>4</sup> Sasaki, in his study of this same azide, obtained the same results. However, he did not believe Kyba's model satisfactorily explained the migration ratio.<sup>9</sup> Instead, he attributes the observed ratio to the total strain energy of each imine system. This argument, however, contradicts Wiseman's findings, since it predicts the imine with a trans azacyclohexene component (**15**) ring system would be more stable than one with a trans azacycloheptene component (**16**). Neither argument satisfactorily explains the experimental findings.

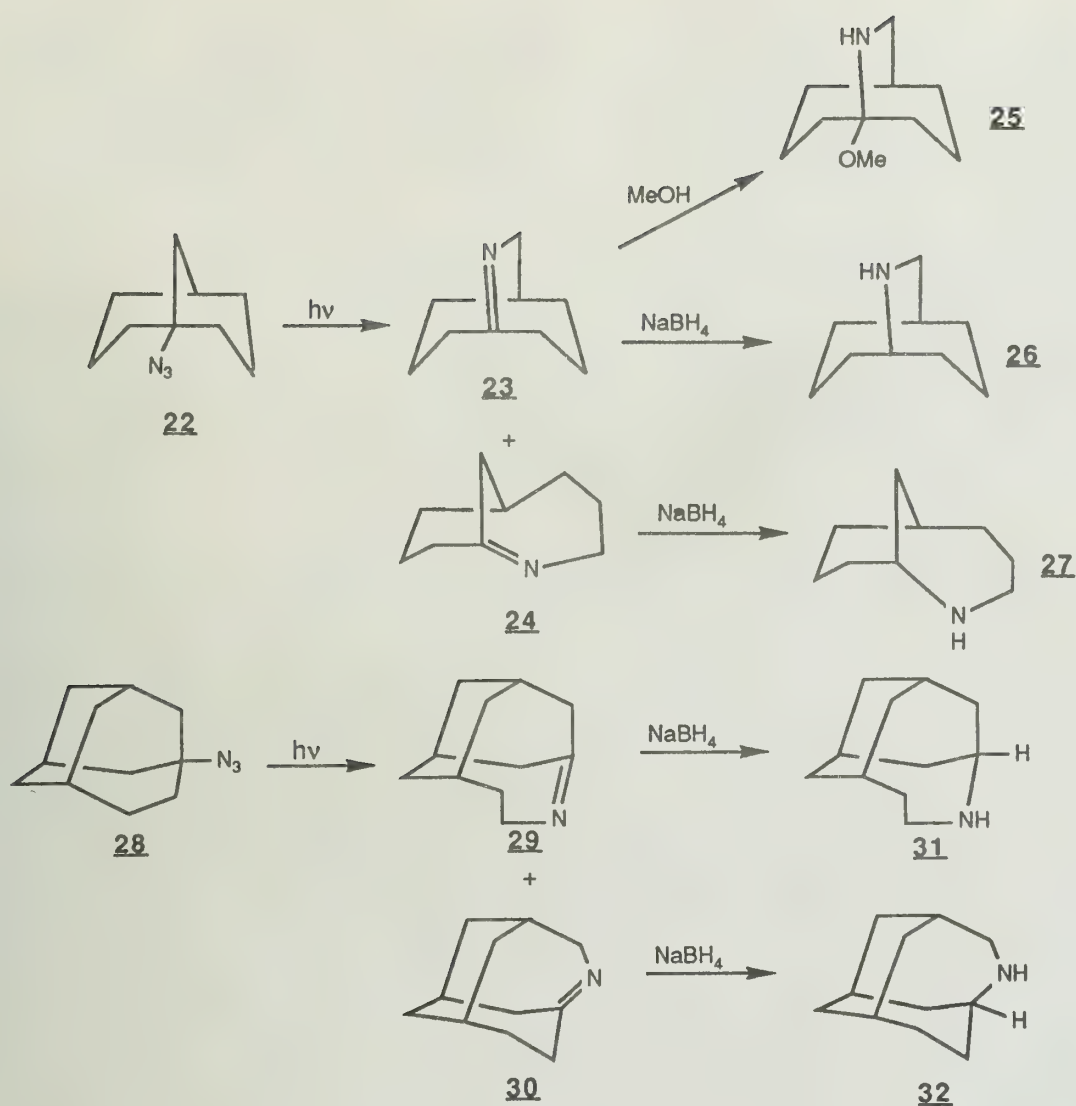


Becker obtained only one product upon photolysis of the unsymmetrical 1-bicyclo[3.2.1]octylazide (**19**) in methanol.<sup>10</sup> He proposed that this adduct (**21**) arose from the more strained imine and thus concluded that the strain must not be felt in the transition state. However, Becker's results must be viewed with caution. The mass balance of the experiment was poor, and there is the possibility that he failed to trap one or both of the more stable imines (**20a** and **20b**). The following work by Sasaki showed this may actually be the case.



Irradiation of 1-azidobicyclo[3.3.1]nonane (**22**) gave particularly interesting results.<sup>6</sup> Photolysis of **22** in MeOH yielded the two possible imines, but only one (**23**) was trapped by MeOH. When an IR spectrum of the crude reaction mixture was recorded after photolysis in methanol, a band at  $1658\text{ cm}^{-1}$  was observed and was assigned as the C=N stretch of the untrapped imine (**24**). Although this imine could not be isolated, when  $\text{NaBH}_4$  was used as a trapping agent, products of both intermediates **23** and **24** were obtained. This shows **24** is formed upon photolysis, but is inert to MeOH. Its stability is consistent with its E-azacyclononene structure. Similar results were found for 3-azidohomoadamantane, **19**.<sup>16</sup> In this case, neither of the imines, **29** and **30**, both of which are E-azacyclooctenes, reacted with MeOH, and the crude photolysis mixture displayed an IR band at  $1650\text{ cm}^{-1}$ . Again, photolysis in the presence of  $\text{NaBH}_4$  formed the amines **31** and **32** as a 1:2 (statistical) ratio in 70% yield.





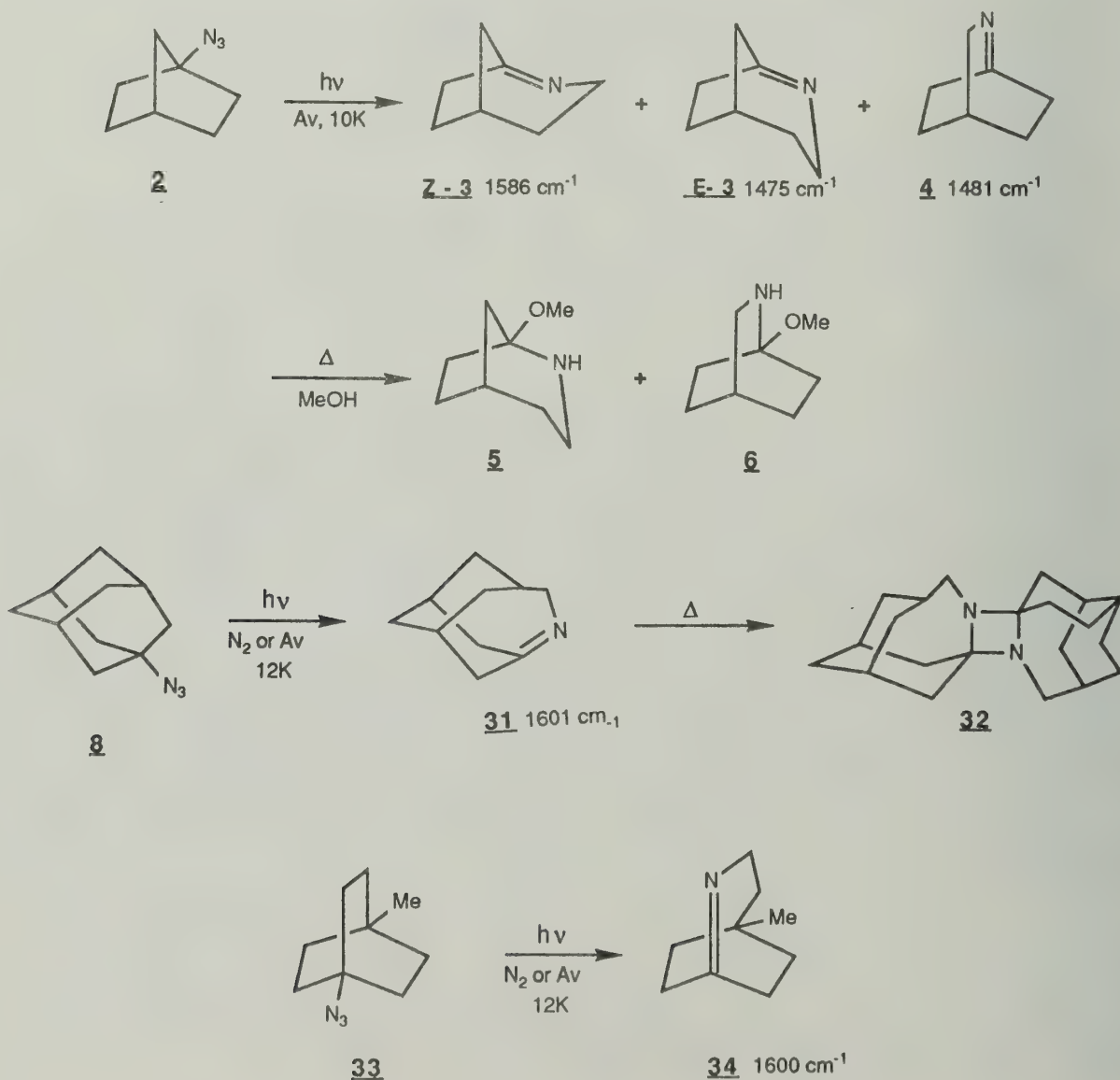
## MATRIX ISOLATION PHOTOCHEMISTRY

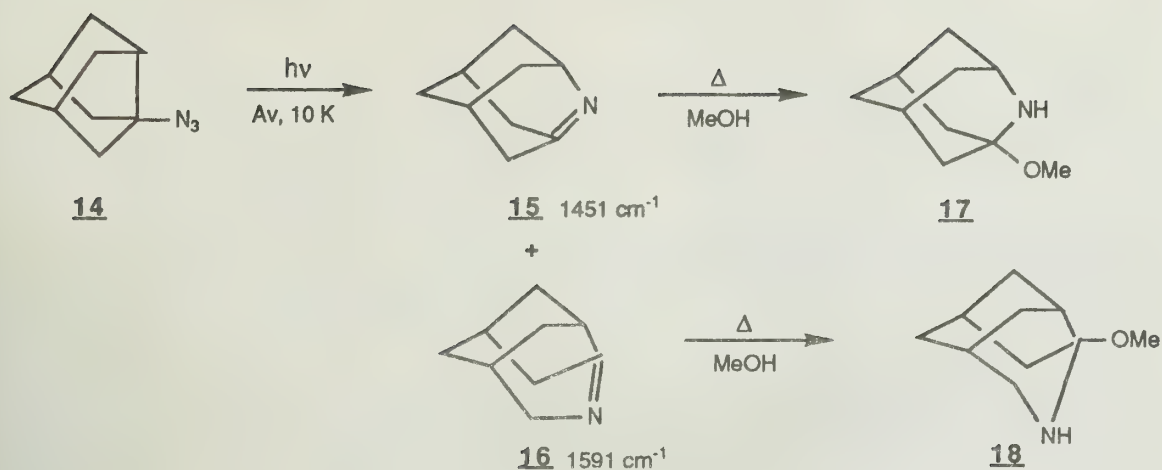
While the bridgehead imine intermediate has been postulated since 1970, only the relatively stable imine (**1**) had been isolated. Matrix isolation photochemistry has recently given the most conclusive evidence for the existence of strained, anti-Bredt imine intermediates. In 1983, three reports appeared almost simultaneously on the matrix trapping of bridgehead imines.<sup>17-18</sup>

Matrix isolation is essentially a technique for prolonging the lifetime of reactive fragments and unstable molecules. The species of interest is trapped at high dilution within an inert rigid host. The inertness of the lattice prevents intermolecular guest-host reactions and rigidity prohibits substrate diffusion and bimolecular reactions.

Michl, who has done the most extensive work, has reported on the matrix photochemistry of 1-azidoadamantane (**8**)<sup>20</sup>, 3-azidonoradamantane (**14**)<sup>21</sup>, and 1-azidonorbornane (**2**).<sup>17,22</sup> Sheridan has also studied **2**, and his results agree with those of Michl.<sup>18</sup> Dunkin and Shields have examined the matrix photochemistry of **8**, as well as that of 1-azido-4-methylbicyclo[2.2.2]octane, **33**.<sup>19</sup>

In all of the matrix studies, the experimental approach was similar. The precursor azides were isolated in solid N<sub>2</sub> or Ar at 10-20K. The matrices were then photolyzed and the UV and IR of the starting material were observed to disappear, with concurrent appearance of new peaks, assigned to the corresponding bridgehead imines. The major IR band assigned to the bridgehead imines are listed below their structures.





Michl used Raman spectroscopy with azides **14** and **8** to show that  $\text{N}_2$  grows in concurrently with the imines. This proves that in these cases the products are formed by loss of nitrogen.

The IR bands at  $\sim 1450\text{--}1600\text{ cm}^{-1}$  were assigned to the  $\nu(\text{C}=\text{N})$  mode of the imines. This was experimentally confirmed by preparing an  $\text{N}^{15}$  isotopically labelled imine. Michl photolyzed a mixture of  $\text{N}^{14}$  and  $\text{N}^{15}$  labelled **14** in Ar and obtained two major IR absorptions for **15** at  $1451\text{ cm}^{-1}$  and  $1432\text{ cm}^{-1}$ . The former was previously observed for an  $\text{N}^{14}$  imine, so the new band was assigned to the  $\text{N}^{15}$  labelled imine. The  $20\text{ cm}^{-1}$  shift between these bands is consistent with the  $\nu(\text{C}=\text{N})$  assignment of this mode. Similar results were observed upon irradiation of  $\text{N}^{15}$  labelled azide **8**.

All the IR bands observed are shifted  $50\text{--}200\text{ cm}^{-1}$  to lower frequencies than the range for typical planar imines ( $1650\text{--}1660\text{ cm}^{-1}$ ). The UV bands are also significantly red-shifted. The spectral shifts to lower frequencies can be accounted for by a weakening of the  $\text{C}=\text{N}$  double bond due to decreased overlap of the p-orbitals resulting from the twist induced in this system by the bicyclic ring system. Michl predicted the  $\text{C}=\text{N}$  twist angle to be  $35^\circ$  for **8**, based on energy calculations for the lowest singlet states of  $\text{CH}_2=\text{NH}$  as a function of twist angle, and the observed UV spectra of **8**. It is also interesting to note that the difference in strain expected for imines contained in different ring sizes is directly reflected in shifts of the IR bands. The IR bands for the imines that are E-azacyclohexene ring systems (e.g., **15** and **16**) fall in a range between  $1450\text{--}1500\text{ cm}^{-1}$  and those in a E-azacycloheptene ring systems (e.g., **31** and **33**) are between  $1550\text{--}1600\text{ cm}^{-1}$ , reflecting the expected greater strain in the smaller ring system.

Further evidence that the matrix isolated species were imines was obtained by allowing these species to undergo controlled intermolecular reactions within the matrix. Photolysis of azides **2**, **8**, and **14** in MeOH doped matrices produced trapped imines which were converted by subsequent warming

to the corresponding methoxyamines. Also, irradiation of azide **8** in a polyethylene matrix produced the imine **31** which was observed to dimerize upon warming to 195K.

After irradiation of all these azides, Michl observed an ESR signal for the triplet nitrene. The signal does not arise from the imine, since the ESR signal could be destroyed by secondary photolysis without affecting the UV or IR signals of the imine products. Also, the nitrene does not appear to be a precursor to the imine since in CO-doped matrices, the isocyanate (a nitrene product) was formed upon warm-up, again without affecting the yield of imine products.

Michl also examined the stereochemistry and chirality of these imines. Both the Z and E isomers of one imine (**Z-3** and **E-3**) derived from azide **2** were observed, and by selective excitation, **E-3** could be photoisomerized to **Z-3**. Furthermore, non-symmetrical imines are chiral, and a CD spectra of **8** was obtained. The imine derived from azide **8** is a chiral molecule, but is produced as a racemic mixture. However, upon irradiation with circularly polarized light, a partial matrix photoresolution can be achieved. This selectivity depletes one optically active isomer, giving an excess of the isomer which absorbs less light ( $\epsilon$  smaller). A CD signal of the same magnitude but opposite sign was obtained upon irradiation with the oppositely polarized light.

## CONCLUSION

The solution work on photolysis of bridgehead azides, especially that conducted by Sasaki and Quast, provided evidence for the existence of bridgehead imines by isolating products that appeared to arise from an intermediate imine. However, it has been the matrix isolation photochemistry that has proven that bridgehead imines are distinct products in the photochemistry of bridgehead azides. All of the matrix work so far has agreed on the assignment of the imine intermediates, mainly via IR spectroscopy. Michl has done much to elucidate other properties of these species. There are still many unanswered questions in this relatively new field. An adequate explanation as to why statistical migration is observed in some cases and not others has not been provided. Also, the question of whether a concerted pathway or a singlet nitrene intermediate is involved in the rearrangement has not been answered, though a concerted pathway is currently favored.



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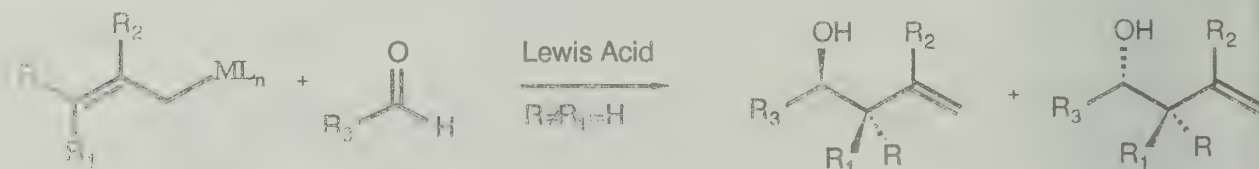
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## STEREOCHEMISTRY AND MECHANISM OF ALLYLMETAL-ALDEHYDE CONDENSATIONS

Reported by Brad R. Henke

February 9, 1987

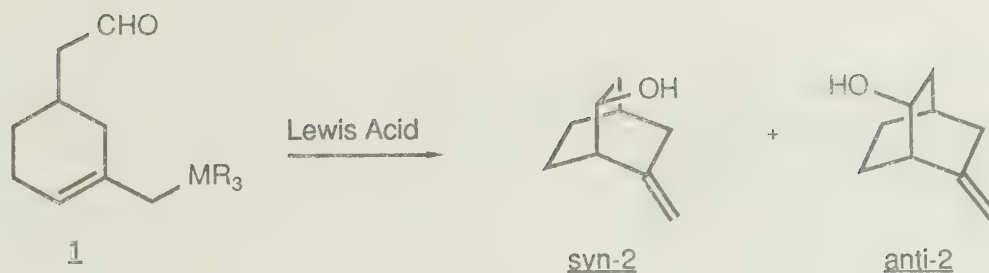
The addition of allylmethyls to aldehydes is a powerful method for controlling stereochemistry in the synthesis of acyclic systems.<sup>1</sup> The reaction (Scheme 1) produces synthetically useful homoallylic alcohols in high yields with a wide variety of metals; among them are silicon,<sup>2</sup> titanium,<sup>3</sup> boron,<sup>1b,4</sup> tin,<sup>5</sup> aluminum,<sup>6</sup> chromium,<sup>7</sup> zirconium,<sup>8</sup> lithium,<sup>9</sup> and



SCHEME 1

One of the most intriguing aspects of this reaction is the dependence of diastereoselectivity on the metal. Lewis acid-catalyzed reactions of crotylstannanes<sup>5a,5b</sup> and crotylsilanes<sup>11</sup> with various aldehydes are syn-selective regardless of the geometry of the crotyl unit. However, reactions of crotyltitanium,<sup>3</sup> crotylchromium,<sup>7</sup> and crotylzirconium<sup>8</sup> compounds are predominantly anti-selective. In addition, methods have been developed for achieving high diastereofacial selectivity in additions of crotylstannanes<sup>12</sup> and allylsilanes<sup>2a,13</sup> to chiral  $\alpha$ - and  $\beta$  alkoxy aldehydes via Lewis acids, producing chelation-controlled products with high levels of asymmetric induction. Enantioselective allylation of aldehydes with optically active allylmethyls has also been investigated.<sup>2b,14</sup>

Although the utility of this reaction has been well explored, mechanistic studies are lacking. Both cyclic<sup>4a</sup> and open<sup>5,11</sup> transition states have been postulated to explain the dependence (or lack thereof) of selectivity on the allylmethyl geometry. Only recently have the role of the Lewis acid and the structure of these complexes in solution been investigated.<sup>15</sup> One approach has been to use model system 1 (Scheme 2) to examine the dependence of transition state geometry as a function of metal, Lewis acid, and reaction conditions.<sup>15c,d</sup> Thorough investigations<sup>16</sup> with 1 ( $\text{MR}_3=\text{SiMe}_3$ ) and  $\text{SnCl}_4$  reveal that the stereochemical course of addition is influenced by concentration, stoichiometry of reagents, and the presence of "dummy ligands" on the  $\text{SnCl}_4$ ; in addition, the solution behavior of the complex between  $\text{SnCl}_4$  and 4-t-butylbenzaldehyde has been studied, and an X-ray structure of this complex has been obtained.



SCHEME 2

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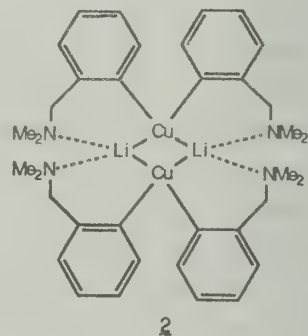
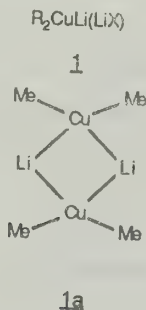
RECENT INVESTIGATIONS ON THE MECHANISM OF REACTION OF LITHIUM  
DIMETHYLCUPRATE WITH  $\alpha,\beta$ -UNSATURATED KETONES AND ESTER

Reported by Lyndon Marble

February 16, 1987

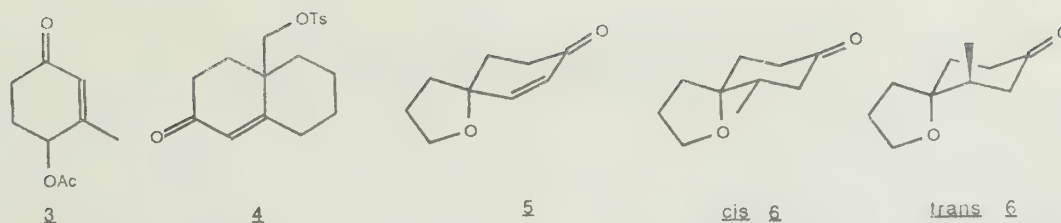
Current investigations into the mechanism of the conjugate addition of lithium dialkylcuprates (Gilman reagents, 1) with  $\alpha,\beta$ -unsaturated ketones have revealed new information about the structure of the reagent, the intermediates on the reaction pathway and the kinetics of the addition.

Molecular orbital calculations<sup>1</sup> have shown that lithium dimethylcuprate, 1a, prefers a square planar arrangement of metal atoms with unequal R-Li and R-Cu bond lengths. van Koten<sup>2</sup> has obtained a crystal structure of the neutral cuprate cluster, 2, which contains an approximately square planar arrangement of metal atoms. This is in contrast to the commonly-accepted tetrahedral structure proposed by House<sup>3</sup>. However, several authors<sup>4</sup> have shown that the structure of 1a can apparently vary in solution depending on choice of solvent, temperature, ratio of MeLi to MeCu and on the presence or absence of LiI.

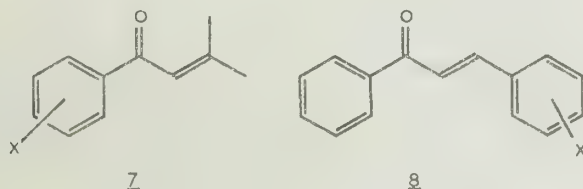


House<sup>5</sup> has proposed that a single electron transfer (SET) is the initial step in the reaction between 1a and enones; the two radicals formed then recombine rapidly to give an intermediate. In support of the SET mechanism, House<sup>6</sup> has observed that double bond isomerization of certain enones occurs in the presence of 1a. House<sup>7</sup> has also calculated the reduction potentials of enones and found that homocuprates have oxidation potentials which are well matched to afford electron transfer. Ruden<sup>8</sup> and Smith<sup>9</sup> examined the reactions of 3 and 4 respectively, with 1a and found that the enones gave reduction products rather than conjugate addition products. Single electron transfer mechanisms were proposed to explain these results.





Ullenius<sup>10</sup> and Corey<sup>11</sup> demonstrated that a Cu- $\pi$  complex is present in these reactions. Corey found that formation of this complex was reversible; by adding TMSCl<sup>12</sup> to a mixture of 1a and 5 he found that *trans* 6 was produced, whereas *cis* 6 was produced in the absence of TMSCl. The trapping of an intermediate leading to *trans* 6 shows that the pathway to *cis* 6 involves a rapid equilibrium between the two Cu- $\pi$  complexes.



Smith and Krauss<sup>13</sup> observed that the reaction of lithium dimethylcuprate with  $\alpha,\beta$ -unsaturated ketones is pseudo first order in ketone. The rates of reaction of 1a with aryl substituted 1-phenyl-3-methyl-2-buten-1-ones 7 and  $\beta$ -aryl chalcones 8 were correlated separately to Hammett's constants and gave  $\rho +1.58$  for 7 and  $\rho = -0.88$  for 8, indicating charge build-up at the carbonyl carbon and charge depletion at the  $\beta$  carbon. These data are consistent with the slowest step being the formation of the Cu(III)- $\beta$  C lithium enolate. Formation of this enolate is preceded by a complex equilibrium which presumably contains species coordinated via lithium to the enone carbonyl.

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# 1,3-DIANIONS IN ORGANIC SYNTHESIS: $\beta$ -LITHIOALKOXIDES AND AMIDES, AND $\alpha$ -LITHIOENOLATES.

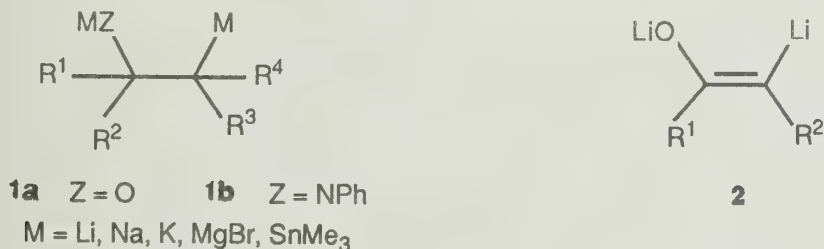
Reported by Diane L. Ridout

February 19, 1987

While ortho-lithiation of aromatic compounds has been studied extensively and is thought to involve precoordination of the lithiating agent to the ortho-directing group, non-aromatic organolithium compounds are also capable of intramolecular coordination.<sup>1</sup> This review will cover the formation and reactions of two such classes of compounds,  $\beta$ -lithioalkoxides and amides (1), and  $\alpha$ -lithioenolates (2).

The reduction of epoxides with lithium in liquid ammonia had long been thought to proceed via  $\beta$ -alkoholate lithium compounds (1a, M=Li); however it was not until 1971 that this was verified by Kaiser through alkylation and deuteration experiments.<sup>2</sup> Since that time, the regiochemistry of epoxide opening,<sup>3</sup> the stereochemistry of reductive alkylation,<sup>4</sup> and the formation of these dianions by trimethylstannyllithium addition<sup>5</sup> have been examined. Reduction of aziridines similarly produces metallated amides (1b).

Compound 1a has also been formed from chlorohydrins by reaction with *n*-butyllithium followed by lithium naphthalenide,<sup>6</sup> or through the trans-metallation of organomercury compounds;<sup>7</sup> chiral chlorohydrins were found to yield chiral dianions.<sup>8</sup>  $\beta$ -Alcoholate and  $\beta$ -amide organometallics have been used to form olefins,<sup>9</sup> 1,2- or 1,3-amino alcohols or diols,<sup>10</sup> and  $\beta$ -amino or  $\beta$ -hydroxy thioethers,<sup>11</sup> as well as a number of other useful compounds.



Another species containing the 1,2-dilithium alcoholate moiety is the  $\alpha$ -lithioenolate 2 which is the tautomer of the  $\alpha$ -ketodianion. Compounds of this type have been made through the enolization of  $\alpha$ -haloketones followed by lithium-halogen exchange,<sup>12</sup> or through the metallation of  $\beta$ -haloenol acetates.<sup>13</sup> Molecular orbital calculations suggest that both the first and second lithiations are favored thermodynamically.<sup>14</sup> Species 2 undergoes Aldol reaction with hindered ketones under conditions where the simple enolate is inert.<sup>15</sup>  $\alpha$ -Bromolithioenolates (2, R<sup>2</sup>=Br), side products of  $\alpha$ -lithioenolate formation, undergo the carbon analogue of the Hofmann rearrangement.<sup>16</sup>  $\alpha$ -Lithioenolates also react with dialkyl chlorophosphates to form  $\beta$ -ketophosphonates,<sup>17</sup> and with chlorotrimethylsilane to form  $\alpha$ -trimethylsilyl ketones.<sup>18</sup>

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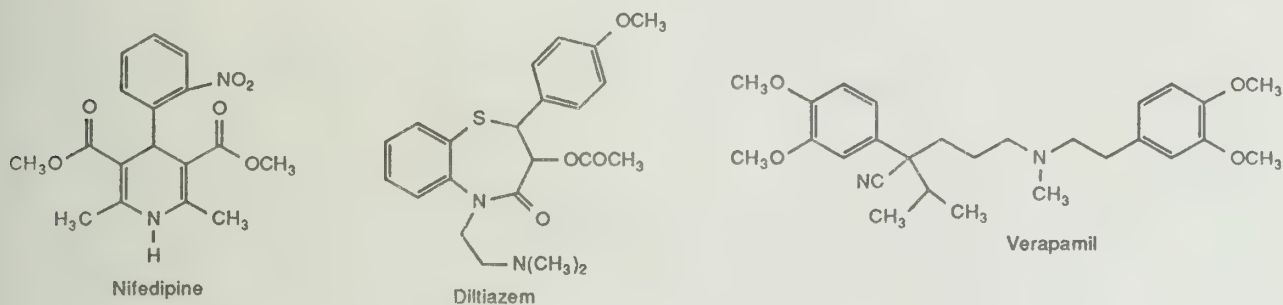


## CHEMISTRY OF DIHYDROPYRIDINE CALCIUM CHANNEL BLOCKERS

Reported by Guy Bemis

February 26, 1987

Several biological mechanisms have evolved for controlling the flow of calcium across cell membranes because of the importance of regulating the calcium concentration gradient between the inside and outside of cells. One such mechanism that has recently received much attention is the voltage-sensitive calcium channel (VSCC).<sup>1</sup> The VSCC, in addition to being regulated by cell membrane potential, can be switched "on" or "off" by three distinct classes of drugs<sup>2</sup> - class I, represented by nifedipine, a 1,4-dihydropyridine, class II, represented by verapamil, and class III, represented by diltiazem (see Scheme 1). These three classes of drugs are distinguished by their interactions at different sites of the VSCC.

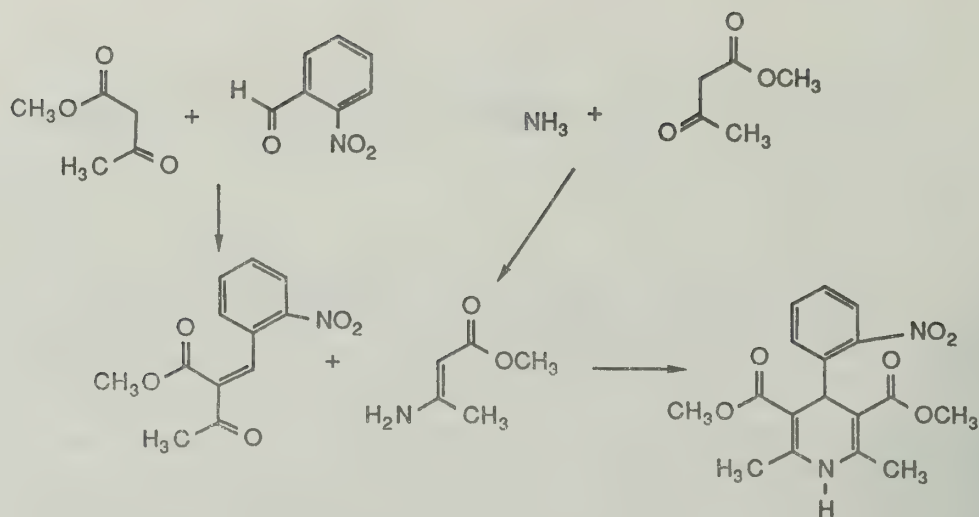


Scheme 1.

The calcium channel drugs are therapeutically important for the treatment of angina and hypertension: By blocking the influx of calcium, cellular  $\text{Ca}^{2+}$ -dependent myofibril-ATPase activity is reduced and less energy is expended for blood vessel muscle contraction<sup>3</sup> - this results in cardiodepression and coronary vasodilation.<sup>1</sup> Because of their therapeutic importance as calcium channel blockers, the 1,4-dihydropyridines (the class I drugs) have been subjected to extensive biological and synthetic study.

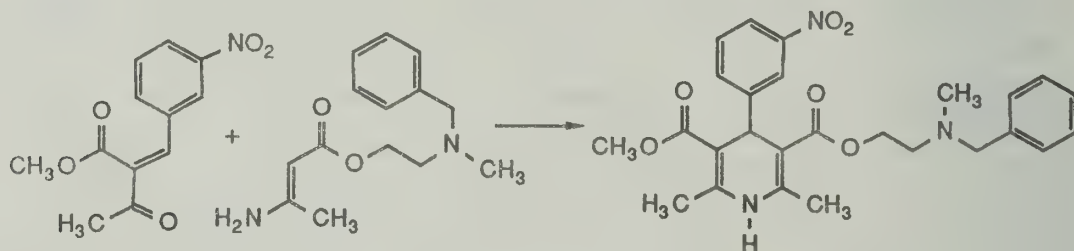
**Synthesis of 1,4-Dihydropyridines**

The first synthesis of 1,4-dihydropyridine-3,5-dicarboxylates was reported by Hantzsch<sup>4</sup> in 1882. In his landmark synthesis, he performed a one-pot condensation of one mole of aldehyde, one mole of ammonia, and two moles of a  $\beta$ -ketoester. The classical Hantzsch synthesis is valuable for the preparation of symmetrically-substituted 1,4-dihydropyridines, as exemplified by the synthesis of nifedipine shown in Scheme 2.



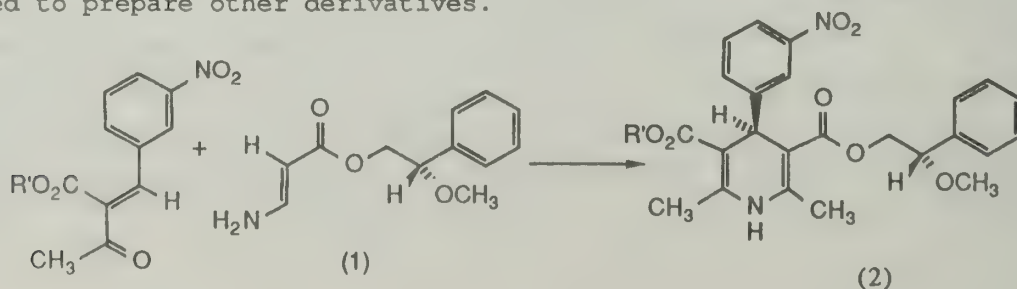
Scheme 2.

Variations of the Hantzsch synthesis have proved fruitful for the synthesis of 1,4-dihydropyridines with unsymmetrical ester substitution. For example, in the synthesis<sup>3</sup> of racemic nicardipine shown in Scheme 3, the pre-formed aralkylidene-acetoacetate from a Knoevenagel condensation is allowed to react with the pre-formed aminocrotonate.



Scheme 3.

Optically active 1,4-dihydropyridines have been prepared by two methods, by resolution of diastereomeric acids<sup>5</sup>, and by synthesis with chiral aminocrotonates. An example of the second method<sup>6</sup>, shown in Scheme 4, starts with the optically active aminocrotonate 1. The Michael cyclization proceeds with high diastereoselectivity to give dihydropyridine 2. Because of the electron withdrawing effect of the methoxy substituent, selective trans-esterification can be used to prepare other derivatives.

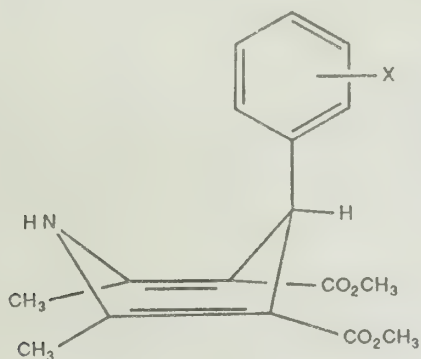


Scheme 4.

Two molecules useful for characterization of the dihydropyridine receptor site have been prepared starting from derivatives of 2: [ $^{125}\text{I}$ ]iodipine<sup>7</sup>, a high affinity and high specific activity 3-(4-hydroxy-5- $^{125}\text{I}$ iodophenyl)propionate derivative, and [ $^3\text{H}$ ]azidopine,<sup>8</sup> a tritium-labeled, photoreactive 4-azidobenzoate derivative.

### Structure-Activity Relationships

X-Ray crystallography has been used to relate the three-dimensional crystal structure of simple 4-aryl-1,4-dihydropyridines to their VSCC blocking abilities.<sup>9</sup> A schematic depiction of the generalized crystal structure for molecules of this class is shown in Scheme 5. The main features to note are the boat conformation of the 1,4-dihydropyridine ring, the "priapic" orientation<sup>9b</sup> of the 4-aryl group, and the orientation of any substituents on the aromatic ring away from the ring nitrogen.



Scheme 5.

### The Triggle Hypothesis

Triggle<sup>9a,b</sup> has chosen  $\Sigma|\tau|$ , the sum of the absolute values of the six torsional angles around the dihydropyridine ring, as an index for predicting the VSCC blocking activity for these compounds. He hypothesizes that the lower the value of  $\Sigma|\tau|$  for a given non para-substituted 1,4-dihydropyridine (i.e., the greater its planarity), the higher its biological activity. Figure 1 shows a graph of  $\Sigma|\tau|$  vs.  $\log(\text{relative activity})$  for several dihydropyridine<sup>9b,c</sup>; activities are expressed as  $(\text{ID}_{50}(\text{nifedipine})/\text{ID}_{50}(\text{compound}) \times 100)$ , so that numbers greater than 100 represent compounds more potent than the standard. Although the relationship holds for the illustrated compounds, the R-value for the linear least squares fit is only 0.85. Furthermore, Miyamae<sup>9e</sup> has questioned the use of this parameter on the basis of structural and biological work on nilvadipine, a compound that is less planar than nifedipine, yet is more biologically active.

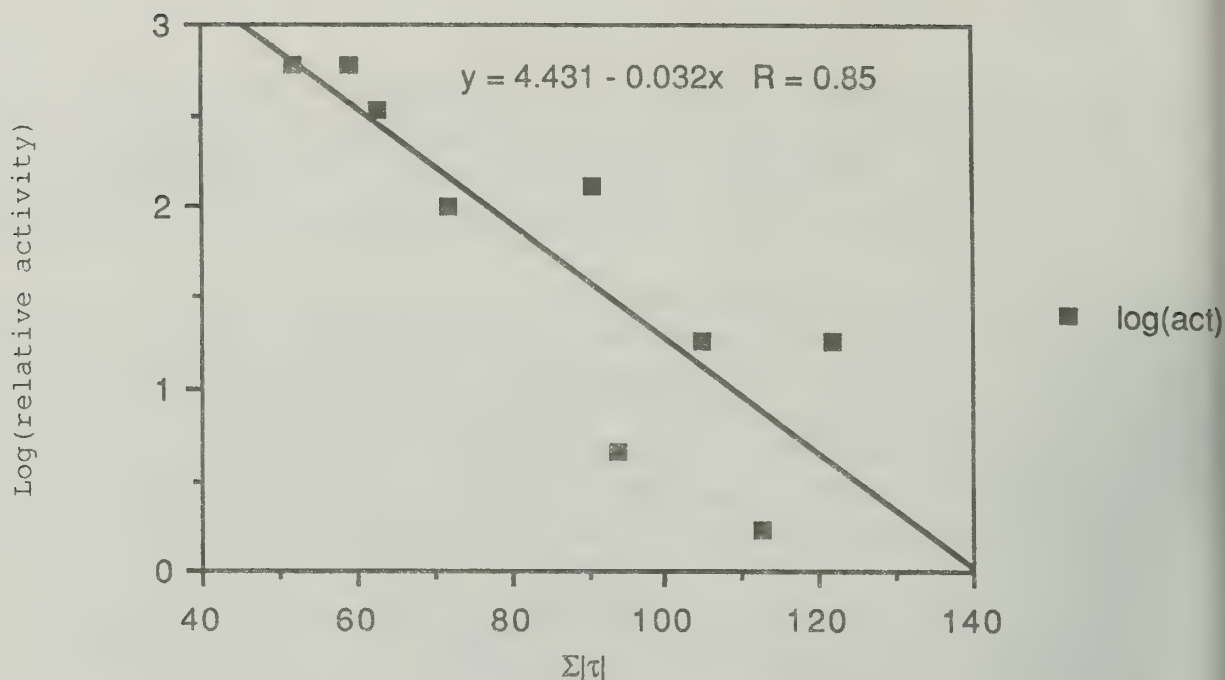


Figure 1. Activity measured against the slow component (tonic response) in guinea pig ileal longitudinal smooth muscle induced by the muscarinic agonist cis-2-methyl-4-[(dimethylamino)methyl]-1,3-dioxalane methiodide.

#### Hansch Analysis

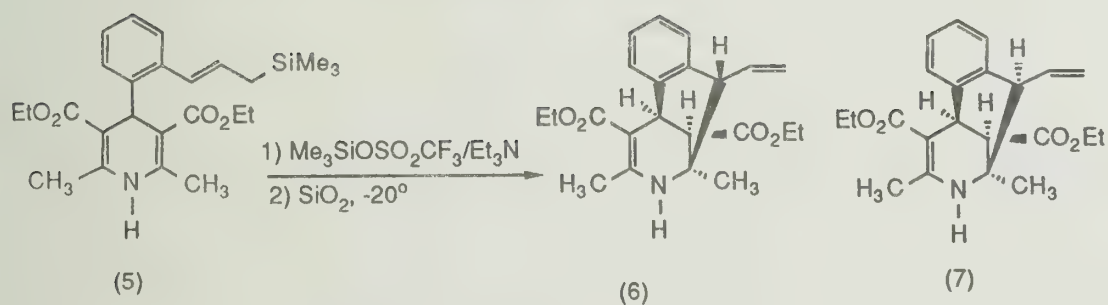
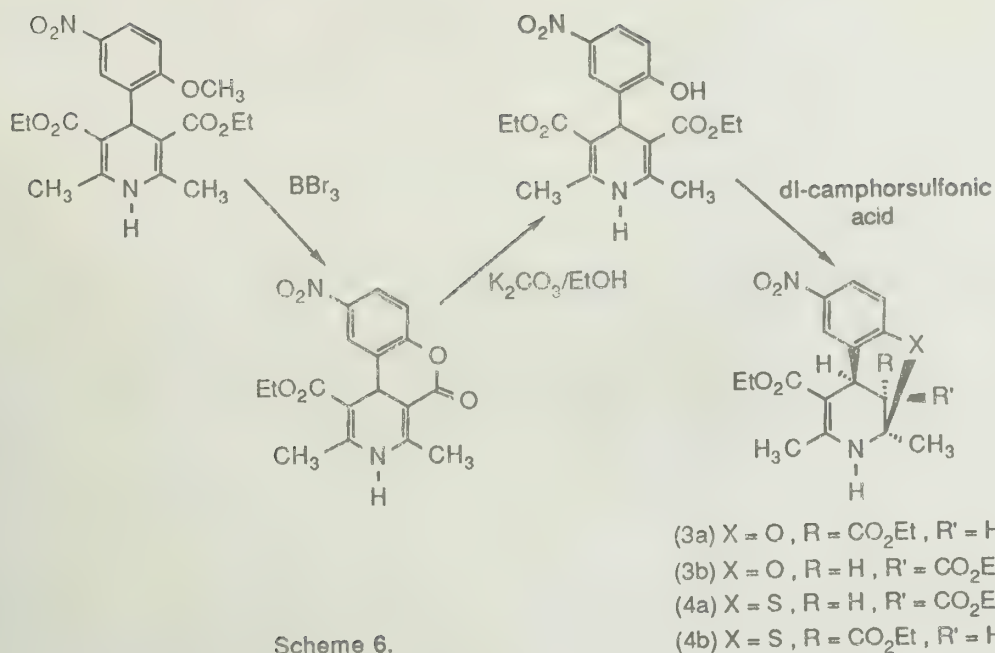
For simple, achiral 4-aryl-1,4-dihydropyridines, the method of Hansch<sup>10</sup> has also been used to determine several quantitative structure-activity relationships (QSAR's). Rodenkirchen<sup>11</sup> has found that for nifedipine derivatives in which the nitro group is replaced with various substituents, the relationship  $\text{Log } 1/\text{EC}_{50} = 5.06 + 0.80 \cdot B_1$  gives a statistically valid correlation, where  $B_1$  is the minimum width of the substituent and  $\text{EC}_{50}$  is measured in isolated, isotonically contracting cat papillary muscles. He has also correlated the biological activity of a series of nifedipine ester derivatives with  $R_m$  and  $\pi$  (the experimental and theoretical lipophilicity of the derivatives) and with  $V_w$ , the van der Waals volume of the ester group.

#### Conformationally-Rigid, Bridged 1,4-Dihydropyridine Analogues

Because the crystal structures of simple 1,4-dihydropyridines show the priapic-aryl-boat features exemplified by the structure pictured in Scheme 5, several research groups have synthesized dihydropyridine analogues in which the 4-aryl group is constrained by an additional intramolecular bond. All of these molecules were synthesized from intermediates prepared using Hantzsch methodology.

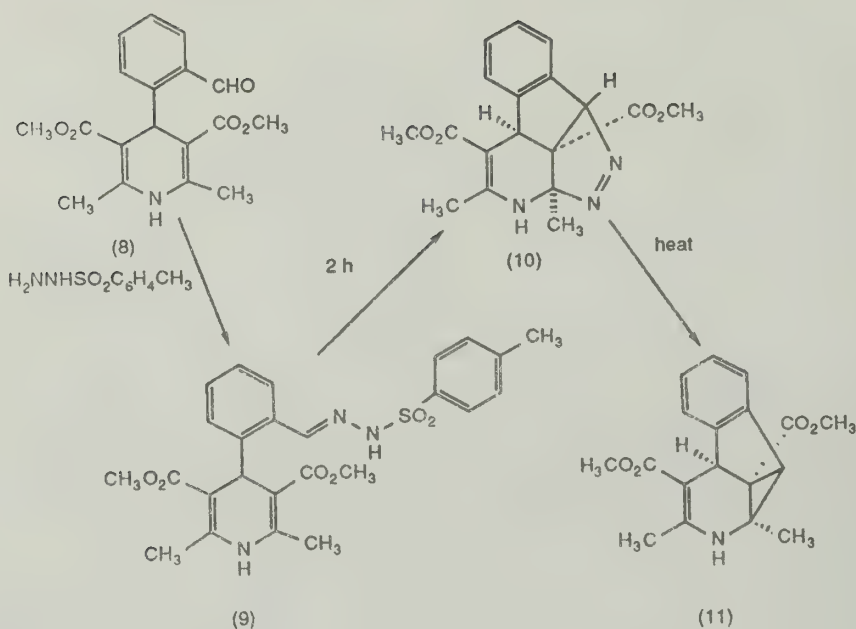
The first series of analogues, developed by Claremon,<sup>12</sup> are bridged from the 2-position of the aryl ring to the 2-position of the dihydropyridine ring by an iminium-ion cyclization process as shown in Scheme 6. The diastereomers **3a** and **3b** (where X = oxygen) were prepared in a 3:2 ratio, and by a slight variation of this procedure, the analogs **4a** and **4b** (where X = sulfur) were also prepared in a 3:2 ratio. In addition, the carbon bridged analogues were prepared by cyclization of the trans-allylsilane **5** to give 57% of **6** along with 5% of **7** as shown in Scheme 7.





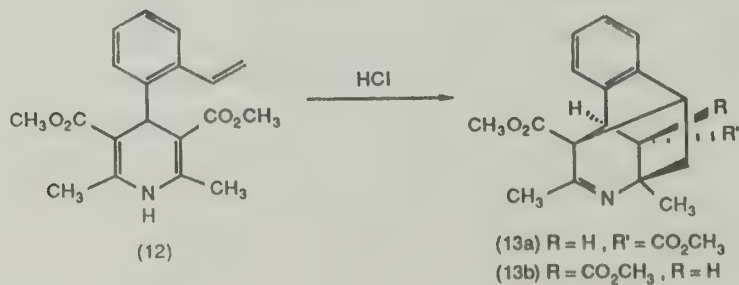
Scheme 7.

The bridged analogues developed by Remy<sup>13</sup> were prepared by intramolecular tosylhydrazone-mediated cyclopropanation, as shown in Scheme 8. Thus, hydrazone **9** was heated to give cyclopropane **11** via pyrazoline **10**.

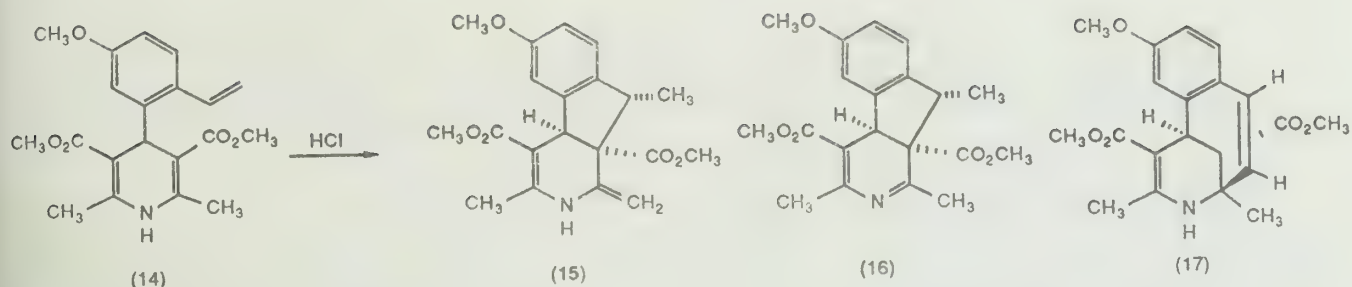


Scheme 8.

Hartman has synthesized several 1,4-dihydropyridines in which the 2-position of the 4-aryl group is abridged to the 2-position of the pyridine ring, and also in which the aryl group is bridged to both the 2- and 5-positions of the pyridine ring. When compound 12 was treated with HCl as shown in Scheme 9, the bis-cyclized diastereomeric products 13a and 13b were obtained in 80% yield in a ratio of 3:2.<sup>14</sup> However, when the 5-methoxyaryl analogue 14 was used,<sup>15</sup> the three monocyclized products (15-17) shown in Scheme 10 were obtained in 86% overall yield; none of the analogous bis-cyclized products were produced. Hartman has also developed similar methods in which the double bond used to bridge the dihydropyridine is included in a thiophene, furan,<sup>16</sup> carbonyl, or thiocarbonyl group,<sup>17</sup> and in which an  $\text{sp}^3$  carbon is placed between the aryl ring and the unit used for bridging.



Scheme 9.



Scheme 10

The bridged compounds that have been described so far will no doubt prove to be interesting probes for the VSCC dihydropyridine receptor site. However, no biological data for them has been published or is yet available for release. If the Triggle hypothesis is valid, then a rough estimate for their biological activity can be given by the graph shown in figure 1. Molecular mechanics calculations done<sup>18</sup> for structures 3b, 11 and 13a indicate that they should have a value for  $\Sigma|\tau|$  which is substantially higher than that for nifedipine.

### Conclusions

Clearly much work remains to be done correlating the biological data obtained from bridged analogues with their structures and the structure of the VSCC dihydropyridine receptor. Once a Hansch-type analysis of a more extensive set of dihydropyridine analogues is developed, it may be possible to propose a generalized model for the dihydropyridine receptor using some new methods developed by Hansch<sup>19</sup>.

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# RHODIUM (II) ACETATE CATALYSIS OF DIAZOESTERCARBONYL COMPOUND DECOMPOSITION: MECHANISM AND SYNTHETIC APPLICATIONS

Reported by Katherine Dowd

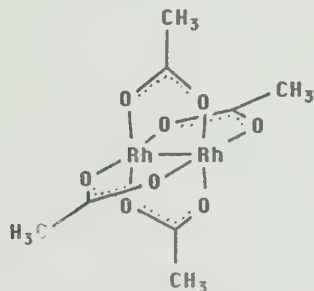
March 2, 1987

The generation of carbenes by decomposition of diazo compounds with transition metals has been known for more than eighty years.<sup>1</sup> Copper (II) catalysts have been the most commonly employed; however, more recently rhodium (II) acetate (1) has been found to effect the same reactions more selectively and under milder conditions. Rhodium (II) acetate has been found to catalyze cyclopropanations, X-H insertions (X= C, N, O, S), and ylide generation. The reactions are believed to occur through the intermediacy of a metal bound carbene or carbenoid species.

## Nature of the Catalyst

Rhodium (II) acetate (1) is a dimeric binuclear compound with a Rh-Rh bond and four acetate ligands.<sup>2</sup> The nature of the Rh-Rh bond is controversial; it is believed to be a single bond by some; however, X-ray crystallography has found it to be much shorter than expected, indicating that it may be a triple bond.<sup>3</sup> Rhodium (II) acetate has one vacant coordination site per metal center and importantly is structurally rigid.<sup>2</sup> It is commercially available from Aldrich at \$27.50/250mg. Other ligands such as trifluoroacetate have also been used, but those will not be discussed here.<sup>2,13</sup>

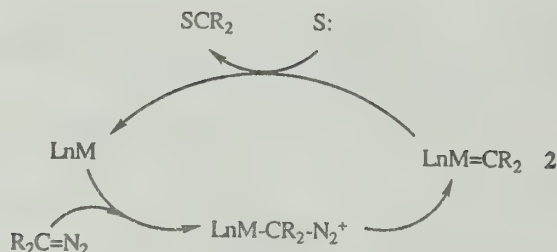
Figure 1: Structure of Rhodium (II) Acetate



## Mechanism of Catalysis

A general mechanism proposed for Rh(II) acetate catalysis is shown in Scheme I.<sup>4</sup> The reactive intermediate is believed to be a carbenoid 2.

SCHEME I  
Mechanism of Catalysis



The reaction occurs by electrophilic attack of rhodium on the diazo compound, followed by loss of dinitrogen to generate the carbenoid 2. The carbenoid is then transferred to an electron rich substrate by oxidative addition. Reductive elimination forms the X-C bond and regenerates the catalyst.<sup>2,5</sup>

A mechanistic investigation by Alonso and coworkers<sup>6</sup> illustrates the electronic nature of the carbenoid and the intermediates in its insertion reactions. This study was carried out with copper(II), which for the most part is analogous to rhodium(II). The reaction of 2-alkoxy-6-methyl dihydropyran 3 with methyl diazomalonate and bis(hexafluoroacetoacetato)copper (II) in refluxing fluorobenzene yields a dihydropyran product 4 (41%) and two diastereomeric cyclopentanes 5 (22%) and 6 (10%) (See Scheme II and Table 1). The cyclopentanes were proven not to arise from the dihydropyran by resubjecting it to the reaction conditions. The results of changing solvent polarity are shown in Table 1. In non-polar solvents, formation of the dihydropyran product is favored by 6:1, whereas in polar solvent formation is disfavored by 10:1.

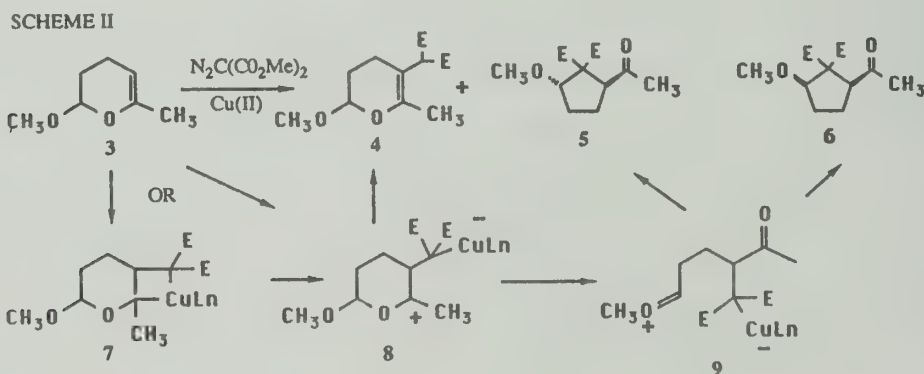


Table 1: Effect of Solvent Polarity on Reaction in Scheme II

Solvent	4: 5, 6	Reaction time	Total Yield (%)
Cyclohexane	6.1	21 hrs	71
Benzene	2.5	2	81
DME	0.13	25	26

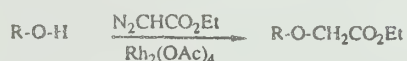
If the reaction is envisioned as proceeding through the zwitterion 8, then in non-polar solvents the dihydropyran is formed directly from 8 by deprotonation. As solvent polarity increases, more of the cyclopentane products (5 and 6) are produced, because 8 begins to partition to the more charge-separated species 9. This dramatic solvent effect suggests that charge-separated intermediates such as 8 and 9 are involved in the product determining steps. However, it is not clear from this study whether the intermediate 8 is formed directly by electrophilic attack of the carbenoid on the olefin or indirectly via a metallocyclic intermediate such as 7.<sup>7</sup>

## Synthetic Applications

### Insertion Reactions

Rhodium (II) acetate is very efficient in catalyzing X-H (X= O, C, N, S) insertion reactions of diazocarbonyl compounds. This was first shown by Reimlinger and co-workers<sup>8</sup> in 1973 with alcohols and ethyl diazoacetate. When a double bond is also present, cyclopropanation is a common side reaction; however, insertion is usually favored by over 8:1.<sup>10</sup> Other transition metals, such as Cu(II)triflate, promote insertions; however, they are far more sensitive to steric effects.<sup>13</sup> (See Table 2).

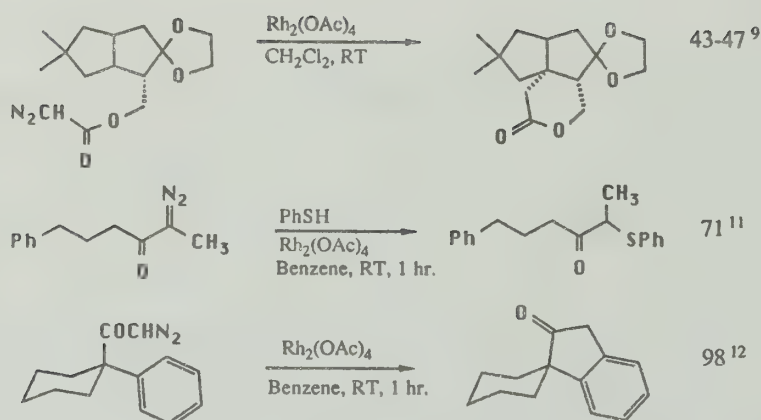
Table 2: R-O-H Insertions



<u>Catalyst</u>	<u>R</u>	<u>%Yield</u>
Rh(II) (Cu(II))	Et	89 (97)
Rh(II)	iso-Prop	83
Rh(II) (Cu(II))	t-Butyl	82 (62)

Intra- and intermolecular carbenoid insertions with Rh(II) acetate have become an increasingly popular method for promoting cyclization to form both hetero- and carbocycles. The catalyst has many advantages: it is selective, conditions are generally mild, and activation at only one site is necessary. Some examples from the recent literature are shown in Scheme III.

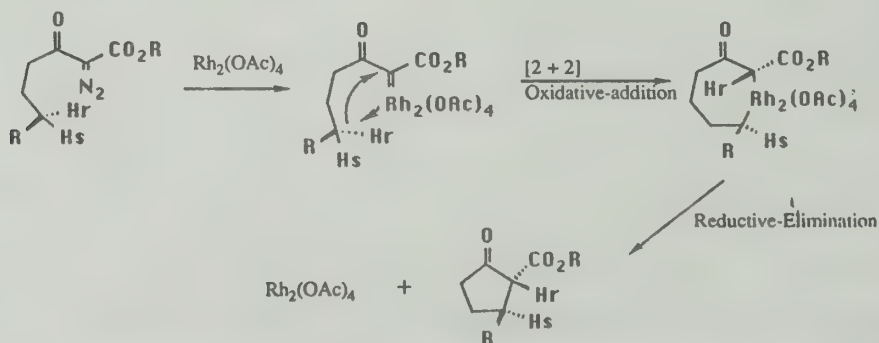
Scheme III



### Scope and Mechanism of Insertion

As shown in Scheme IV, the mechanism of insertion involves a [2 + 2] oxidative addition of the rhodium carbenoid and an X-H bond to form a rhodium containing metallacycle. The oxidative-addition step is rate determining and is probably best described as a two stage concerted [2 + 2] process by Dewar's definition.<sup>14</sup> That is, bond formation is not synchronous, but, stereochemistry is retained. The stereochemical evidence for this will be discussed later. In order for the oxidative addition to occur, the Rh-carbene bond must be colinear with the bond into which it is inserting. As will be shown, this is a major factor in determining the site of intramolecular insertion and the ring size. Another factor that determines ring size is the preference of the  $\alpha$ -carbenoid- $\beta$ -keto ester to remain syn-planar.<sup>15</sup> Taber has shown that insertion proceeds with retention of configuration, as shown in Scheme IV.<sup>16</sup> Thus, reductive elimination, which also proceeds with retention of configuration yields the X-C bond and regenerates the catalyst.

SCHEME IV



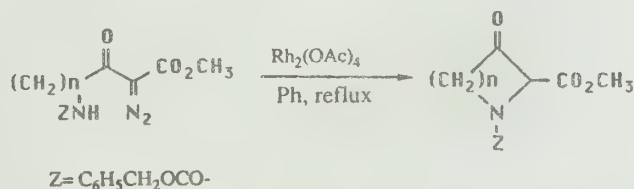
### Formation of Heterocycles

Rapoport and co-workers<sup>17</sup> have studied intramolecular N-H, O-H, and S-H insertion reactions in terms of the ring size formed as well as the effects of



solvent, temperature, and catalyst concentration. Ring size was examined by preparing a series of  $\alpha$ -diazo- $\beta$ -keto ester alkyl carbamates; cyclizations were carried out in benzene with 0.6 mol %  $\text{Rh}_2(\text{OAc})_4$  at 80-90° C. As shown in Table 3 there is a strong preference for the formation of four-, five-, and six-membered rings. The five-membered carbocycle is formed exclusively in preference to the seven-membered ring heterocycle.

Table 3

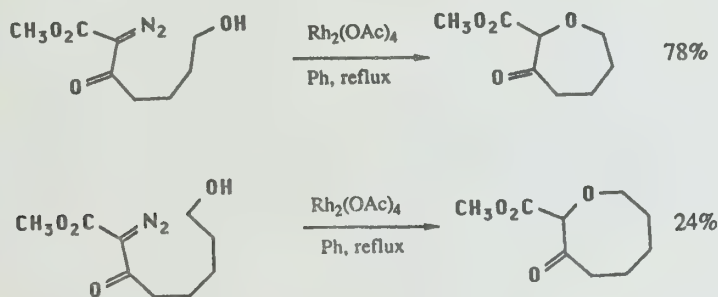


<u>n</u>	<u>Ring size</u>	<u>%Yield</u>
1	4	quant.
2	5	90
3	6	69
4	7 (5)	0 (39% carbocycle)

Recalling the constraints on ring formation and realizing that the nitrogen of a carbamate is an  $\text{sp}^2$  center, one can see by building models the difficulty in achieving proper overlap with the N-H bond for the seven-membered ring closure. Closure also requires that the  $\alpha$ -carbenoid- $\beta$ -keto ester be forced out of planarity. There have been no reported attempts of insertions into N-H amino bonds.

In contrast to Rapoport's conclusions about the preference for the formation of five-membered rings in the carbamate N-H insertion reaction, Moody and co-workers<sup>18</sup> have recently reported the synthesis of seven- and eight-membered cyclic ethers in good yields (See Scheme V). Moody does not report any carbocyclic ring formation.

SCHEME V

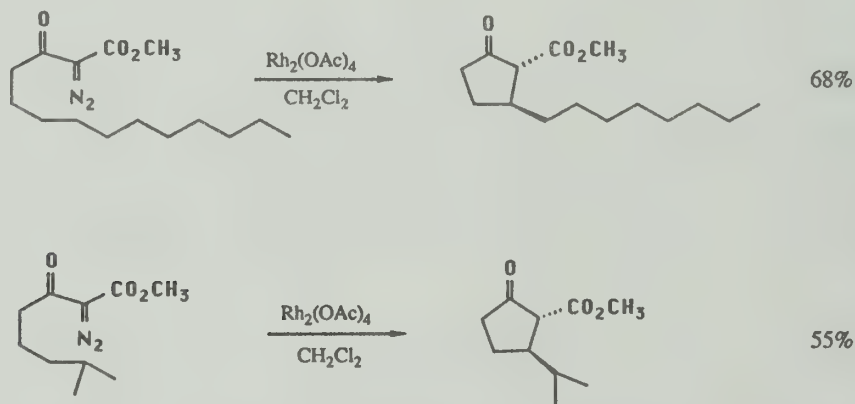


An explanation for the disparity between Rapoport's and Moody's results has already been alluded to: in Moody's case, the hydroxyl is an  $sp^3$  center, making overlap easier and preventing distortion of the ketoester system. Perhaps more importantly, the O-H bond is more electron-rich than the carbamate N-H bond. Moody's result for formation of the eight-membered ether is very impressive, considering the difficulty which has been documented by Illuminati and Mandolini for eight-membered ether formation by traditional methods.<sup>19</sup> The same ring forming reactions should be possible for thiols and amines.

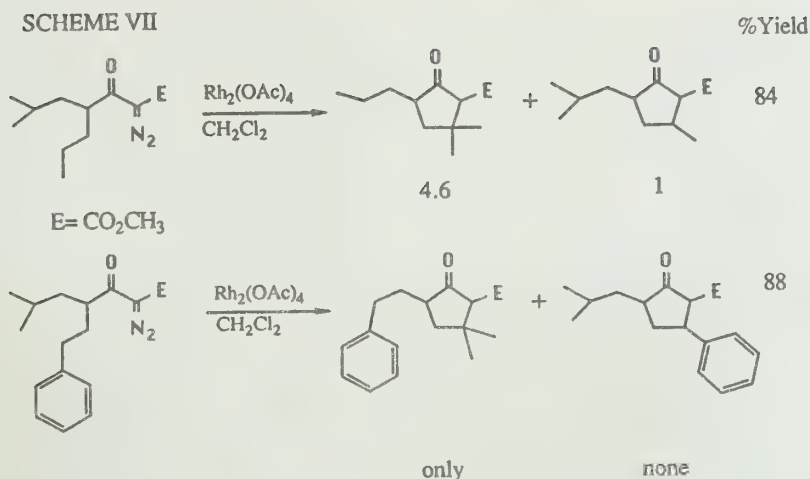
### Formation of Carbocycles

Taber<sup>4</sup> recently investigated steric and electronic effects on the formation of cyclopentanones by C-H insertion. He had previously reported rhodium-mediated carbene insertions into methylenes and methines, noting the strong preference for formation of five-membered rings (See Scheme 6)<sup>20</sup>.

SCHEME VI

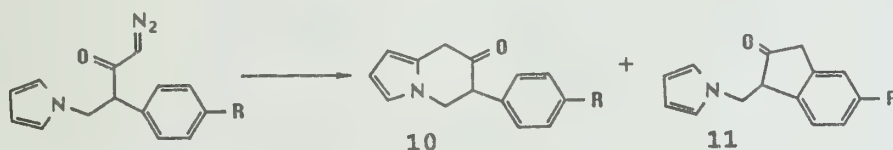


Through a series of intramolecular competition reactions he determined insertion preferences to be methine > methylene > allylic > benzylic > methyl (See Scheme VII). Thus as in the heteroatom cases the carbene prefers to insert at the more electron rich C-H bond. This preference appears to be more important than certain steric effects: based on the [2 + 2] mechanism proposed earlier one might expect that the bulkiness of the methine center combined with the bulky acetate ligands would prevent sufficient overlap of the carbenoid and the C-H bond. However, the major product observed is that of the methine insertion.



Further evidence for insertion dependence on electron density is illustrated by work of Jefford and coworkers<sup>21</sup>. N-Phenylethylpyrroles are cyclized to yield indolizinones 10 (resulting from insertion into the pyrrole C-H bond) and indanones 11 (resulting from insertion into the phenyl C-H bond) (See Table 5). The ratio of 10/11 is dependent on the nature on the phenyl substituent, R. When R is electron donating, such as methoxy, the phenyl ring is electron rich and competes with the pyrrole for insertion. However, when R is electron withdrawing, such as nitro, the pyrrole insertion product is formed exclusively.

Table 4



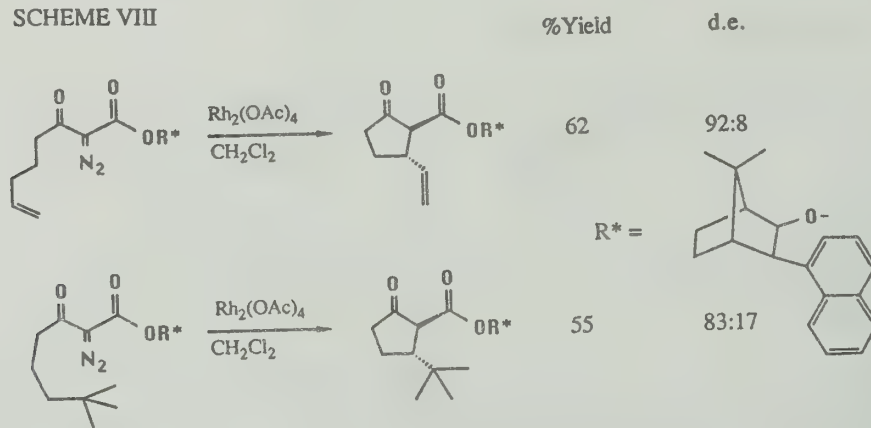
R	<u>10/11</u>
H	6
OCH <sub>3</sub>	3.5
NO <sub>2</sub>	all

### Enantiomeric Ring Construction

Taber has found that five-membered rings can be constructed enantiomerically by two methods. Since insertion occurs with retention of absolute configuration, one can obtain enantiomerically pure products by starting with optically pure starting material.<sup>16</sup> The second method uses a

chiral auxillary to bias the face onto which insertion will occur.<sup>22,15</sup> This was accomplished by use of a bulky chiral ester group; in the best case a diastereoselectivity of 92:8 was obtained (See Scheme VIII).

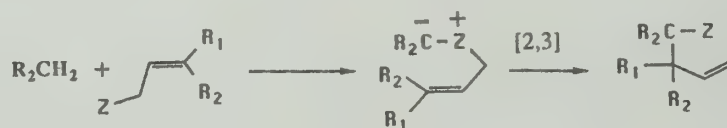
SCHEME VIII



### Generation of Ylides

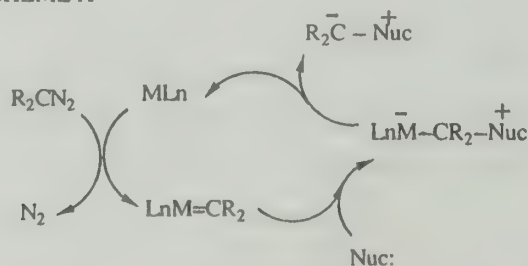
Rh(II) has been used to generate ylides from diazocompounds and allyl sulfides<sup>23</sup>, amines<sup>23</sup>, halides<sup>23</sup> acetals<sup>24</sup>, thioketals<sup>24</sup>, and ethers<sup>25a,b</sup>. After ylide generation, the symmetry-allowed [2,3] sigmatropic rearrangement can occur (See Scheme IX). Cu(II) also catalyzes ylide generation and rearrangement. Rh(II), however, requires much lower temperatures, and competitive reactions such as cyclopropanation and Stevens [1,2] rearrangement are suppressed<sup>23</sup>.

SCHEME IX



The mechanism of ylide generation differs from that of insertion because a labile X-H bond is not involved. Instead, ylides form by nucleophilic attack of the heteroatom on rhodium, followed by reductive elimination (See Scheme X).<sup>23</sup> Doyle believes that the metal does not participate in the [2,3] sigmatropic rearrangement because he finds the same ratio of diastereomers under metal-catalyzed reaction conditions as under base-catalyzed conditions.

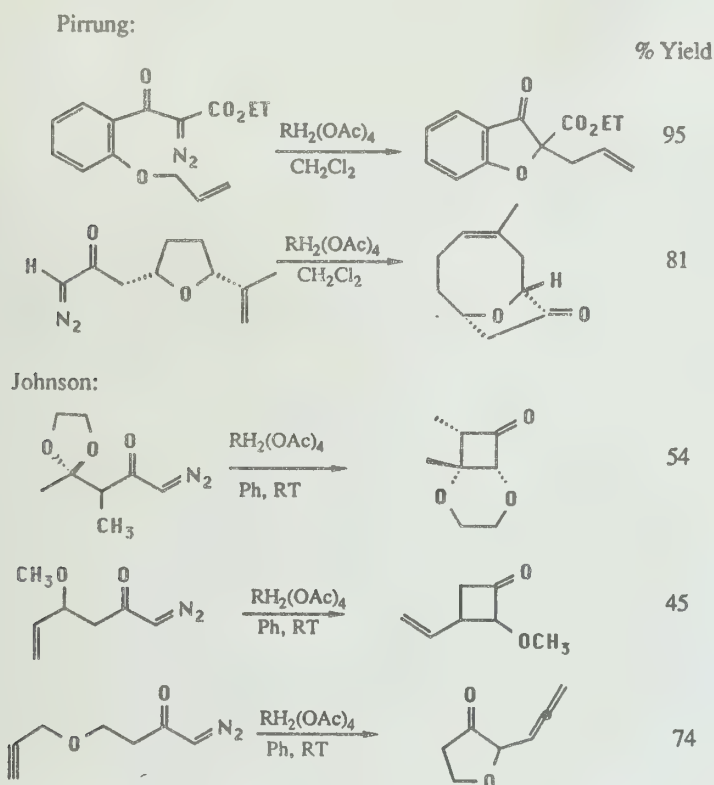
SCHEME X





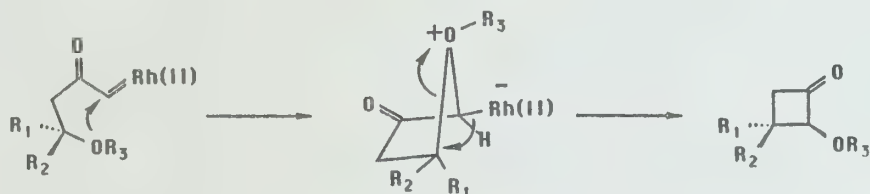
Most of the reactions reported by Doyle<sup>23</sup> have involved intermolecular generation of ylides, but recently Pirrung<sup>25a</sup> and Johnson<sup>25b</sup> have reported intramolecular generation of oxonium ylides. Pirrung reports the formation of five-, six-, and eight-membered ethers (See Scheme XI) in high yield, by intramolecular ylide generation followed by [2,3] sigmatropic rearrangement. Johnson finds that intramolecular generation of oxonium ylides followed by rearrangement is a convenient way to prepare cyclobutanones.

## SCHEME XI



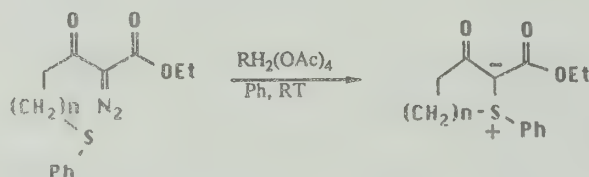
He proposes the mechanism shown in Scheme XII because there is complete retention of configuration the quaternary center. However, formation of a metallocycle followed by reductive elimination would also preserve absolute configuration.

## SCHEME XII



Intramolecular generation of sulfonium ylides has also been reported recently by Davies <sup>26</sup> Their findings are consistent with previous reports that five-, six-, and seven-membered rings are produced in good yields but that C-H insertion to give five-membered carbocycles proceeds in preference to larger ring formation.

Table 5



n	Ring Size	%Yield
1	5	69
2	6	67
3	7	45
4	8	(64% C-H insertion)
5	9	(71% C-H insertion)

## Conclusion

Rhodium (II) acetate catalyzes synthetically useful insertion reactions and ylide generation leading to small and medium membered hetero and carbocycles. Both reactions occur through the rhodium carbenoid that undergoes oxidative addition to form a metallocycle followed by reductive elimination, both being stereospecific. Insertion reactions are believed to occur by a two stage concerted [2 + 2] cycloaddition reaction, whereas ylide generation results from nucleophilic attack at the metal end of the carbenoid.

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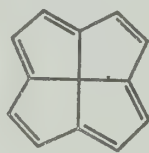
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SQUASHING THE TETRAHEDRON: THEORETICAL AND SYNTHETIC APPROACHES  
TO PLANAR TETRACOORDINATE CARBON

Reported by Martin B. Wolk

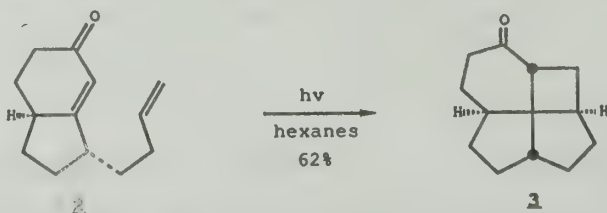
March 5, 1987

One of the basic concepts of modern organic chemistry is that a tetracoordinate carbon atom adopts a tetrahedral geometry. Conformational analysis of methane shows that planar and pyramidal states are inaccessible without bond cleavage.<sup>1a-c</sup> With these and other studies in mind, Hoffmann proposed in 1970 several compounds likely to contain planar or squashed tetrahedral geometries, as one of three types of "novel stabilized systems".<sup>2</sup> Planar tetracoordinate carbon requires a peculiar hybridization for which stabilizing ligands would have to donate electron density through the sigma system and accept through the pi system. Primary candidates, such as **1**, consist of annulenes with a central carbon atom.<sup>3</sup>



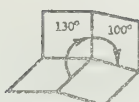
**1**

Early synthetic attempts toward planar molecules concentrated on the related saturated systems. Cumbersome IUPAC nomenclature was avoided with common names such as windowpane, tetraquinacane, and staurane before the term [m.n.p.q]fenestrane fell into general acceptance (where m,n,p,q are ring sizes about the central carbon atom). The first synthetic success was Georgian's 1972 preparation of a [6.5.5.4]fenestrane ketone **3** using a [2+2] photoaddition as the key ring closing reaction (Eqn. 1).<sup>4</sup> Subsequently,



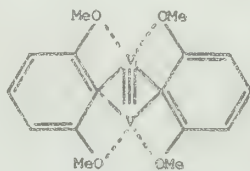
several groups have described the synthesis of fenestrane systems, including substituted and unsubstituted [5.5.5.5], [4.5.5.5], [4.4.5.5], and [4.4.4.5]fenestranes.<sup>5-9</sup> Even with this concerted effort, it was twelve years before the parent [5.5.5.5] hydrocarbon was prepared.<sup>10</sup> (It is interesting to note that the tetraaza analog can be synthesized in one step from available materials).<sup>11</sup> Experimental and theoretical evidence shows that even the most strained of the fenestranes **4** has a geometry about the central carbon that is approximately tetrahedral, with the strain distributed throughout the molecule.<sup>8</sup> Recent efforts have concentrated on the synthesis of more rigid





A

systems although little progress has been made.<sup>6,12-14</sup> However, even these targets have failed recent theoretical tests for planarity.<sup>15,16</sup> To date, no planar tetracoordinate hydrocarbons have been synthesized, although organometallic compound **5** does contain a carbon which has technically met the requirements for tetravalent planarity.<sup>17</sup>



5

(partial structure)

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## THE SYNTHESSES OF TYRANDAMYCIN A

Reported by John Gerlits

March 9, 198

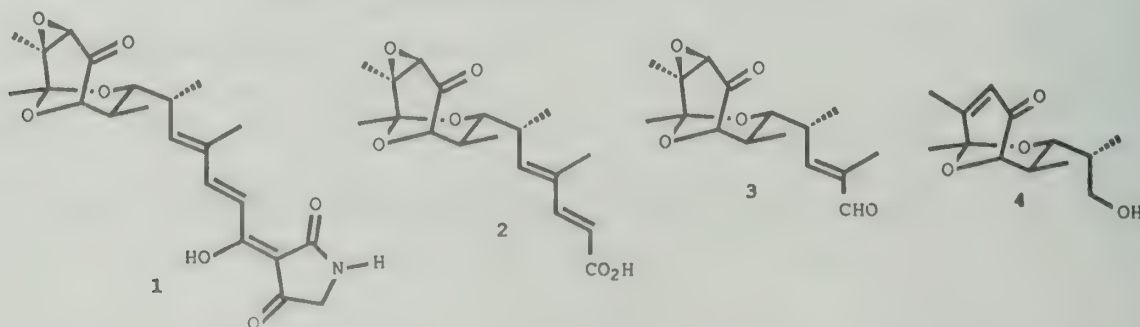
## Introduction

The antibiotic tyrandamycin A<sup>1</sup> 1 was one of the first discovered members of a growing family of complex 3-dienoyl tetramic acids which are of interest because of biological properties which differ from those of the simpler 3-acyl tetramic acids. Included in this group are tirandamycin B,<sup>2</sup> streptolydygin,<sup>3</sup> nocamycin,<sup>4</sup> and Bu-2313 A and B.<sup>5</sup> Tyrandamycin A was isolated from the culture broth of Streptomyces tirandis.<sup>1</sup> X-ray determination of the structure of a derivative established the absolute configuration as shown.<sup>3</sup> These antibiotics all contain a planar enolic dienoyl tetramic acid linked to a functionalized bicyclic ketal, a structural feature which could contribute to the biological activity. Tyrandamycin A exhibits antibacterial activity, is a potent inhibitor of bacterial DNA-directed RNA polymerase, and interferes with oxidative phosphorylation.<sup>2,6</sup> Much of the synthetic activity has focused on tyrandamycin A, because of its activity and because it will serve as a stepping stone to the more complex congeners.

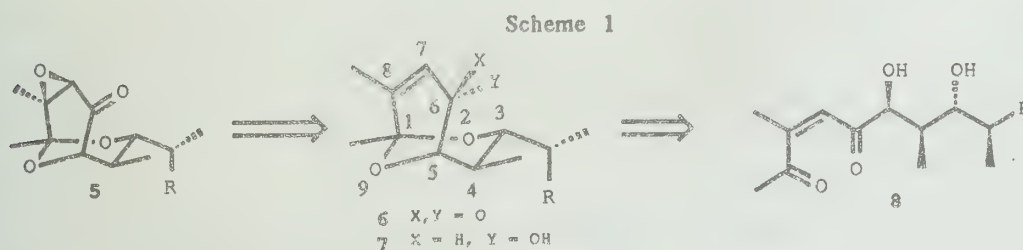
## Key Structural Features

The synthetic methods which have been developed may be discussed in several parts, according to the major structural features of tyrandamycin A. There are similarities in the basic strategies: First, the bicyclic ketal is formed and its functionality is elaborated; this is followed by homologation of the unsaturated side chain, and finally attachment of the tetramic acid unit. This report will focus on the attachment of the tetramic acid and the formation of the bicyclic ketal.

Key intermediates in some of the syntheses were tyrandamycic acid 2, the aldehyde 3, and the "Ireland alcohol" 4. The acid 2 is the periodate degradation product and the aldehyde 3 is obtained upon ozonolysis of tyrandamycin A.



Of the seven stereocenters in the 2,9-dioxabicyclo[3.3.1]nonane system **5** (Scheme 1), three can be easily controlled. Two of the stereocenters are contained in the epoxy moiety, which has been introduced at various stages of the synthesis to a bicyclic enone **6**, using *t*-BuOOH/Triton B/benzene<sup>7,8</sup> or *t*-BuOOH/DBU/THF.<sup>9</sup> The enol **7** could also be epoxidized with MCPBA/CH<sub>2</sub>Cl<sub>2</sub>.<sup>10</sup> The epoxidation occurred in all cases with high *exo*-face selectivity. The relative stereochemistry of the ketal carbon C-1 is controlled by the stereocenter at C-5.



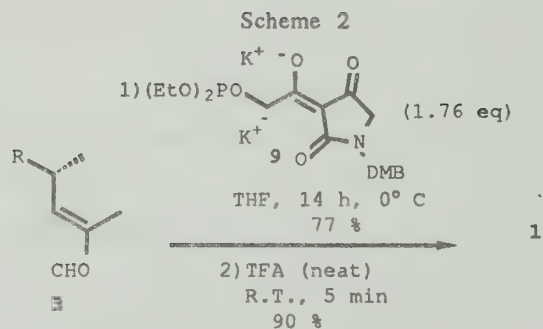
The bicyclic ketal can be unfolded to reveal a latent 1,4-enedione **8**, and it may be formed from an acyclic compound of that general structure. A stereoselective sequence must then be used to form the four remaining contiguous asymmetric centers. The formation of this 2,4-dimethyl-1,3-alkanediol system is a problem of great current synthetic interest.<sup>11</sup>

While it was a simple matter to elaborate the functionality of an appropriately substituted 1,4-enedione to the  $\alpha,\beta$ -epoxy ketone **4**, more elaborate modifications were necessary when a 1,4-dione or some other system was used to form the bicyclic ketal.

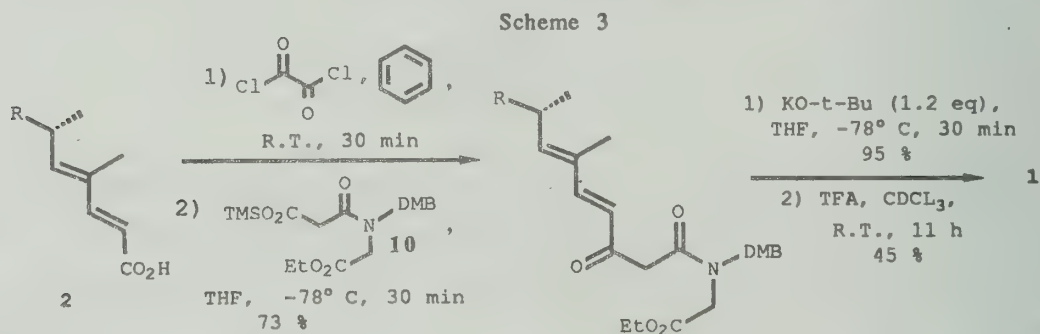
#### Attachment of the Tetramic Acid

A number of strategies have been investigated for the attachment of the tetramic acid to the dienoyl side chain of the bicyclic ketal. Direct alkylation of the sodium, lithium, ethoxymagnesium, or thallium enolates of a tetramic acid with a dienoyl halide such as sorbyl fluoride tends to give mainly *O*-acylated tetramic acids.<sup>12</sup> 3-Acetyl tetramic acids may be synthesized by the rearrangement of an *N*-acetoacetyl aspartimide in the presence of base, but the scope of the reaction is limited.<sup>13</sup>

Boeckman<sup>9</sup> and DeShong<sup>10</sup> utilized the dianion of an activated tetramic acid, **9** (Scheme 2); Boeckman's preparation involved a Dieckmann condensation of a  $\beta$ -keto amide. The dianion **9** was then condensed with the aldehyde **10**.



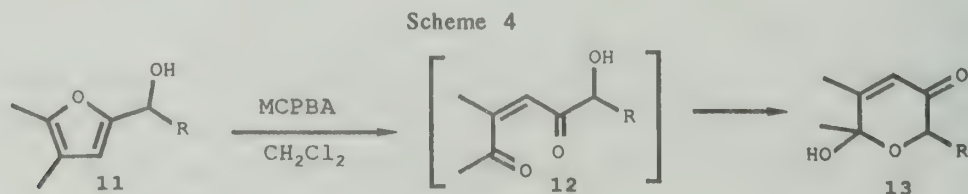
Bartlett also utilized a Dieckmann condensation to prepare the tetramic acid (Scheme 3). The condensation, accomplished with KO-t-Bu, followed the attachment of the bicyclic ketal by acylation of the malonamidate **10** with the acid **2**.



The condensation could not be effected when there was no substituent on the tetramic acid nitrogen. Hydrolysis of the 2,4-dimethoxybenzyl (DMB) group provided racemic **1**. Yields for the deprotection of N-(2,4-dimethoxybenzyl)-tirandamycin A were variable (46-90%), depending on the conditions, with DeShong reporting the highest yield.

### Synthesis of the Bicyclic Ketal

Several of the syntheses were based on the addition of a furan, a latent 1,4-enedione, to an aldehyde. The furan **11** can then be oxidized with MCPBA to give the 1,4-enedione **12** (Scheme 4), which cyclizes to a hemiketal **13** under the acidic conditions.<sup>14</sup> Other methods of oxidation include  $\text{Br}_2/\text{MeOH}$  followed by acid hydrolysis,<sup>15</sup> PCC,<sup>16</sup>  $\text{I}_2$ ,<sup>17</sup> or electrolysis.<sup>18</sup>

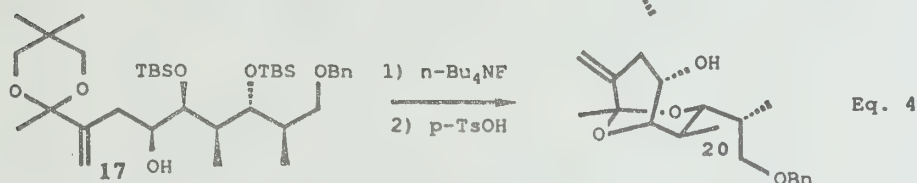
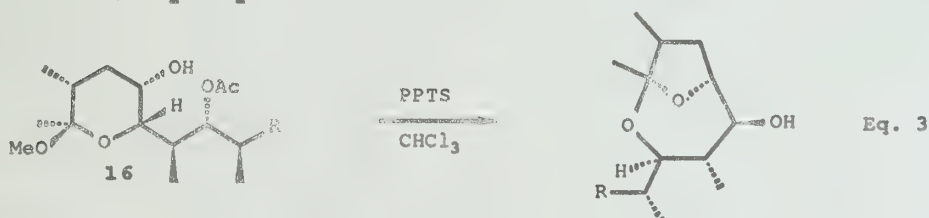
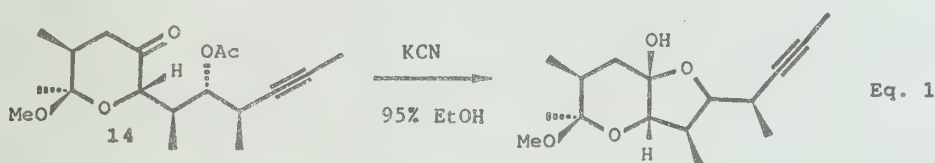


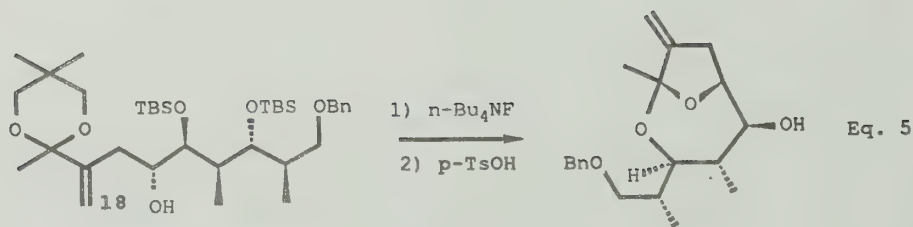


### Prerequisites for Cyclization

It has generally been assumed that the bicyclic ketal is the thermodynamically and kinetically favored product, so that it can be formed in a one step process from an acyclic compound. However, problems were encountered in the cyclization of some systems. In those cases in which a monocyclic methoxy ketal was first formed, cyclization could sometimes be effected by release of the other hydroxy group, forming the bicyclic ketal in a two step process. Other modes of cyclization are also possible.

Bartlett found that the methoxy ketal 14 cyclized in an alternate mode (Eq. 1). This problem may be solved by reduction of the ketone at C-6. However, the hydroxy group at C-6 may then participate in yet another mode of cyclization. The stereochemistry of that hydroxy group appears to control the mode of cyclization: The isomer with the  $\beta$ -OH 15 cyclized in the desired mode (Eq. 2); the isomer with the  $\alpha$ -OH 16 in an alternate mode (Eq. 3). With a similar substrate, Kelly<sup>19</sup> found that the isomer with the  $\alpha$ -OH 17 (TBS = t-BuMe<sub>2</sub>Si) cyclized in the desired mode (Eq. 4), while the isomer with the  $\beta$ -OH 18 cyclized in the alternate mode (Eq. 5). Kelly provided no spectral data to support his assignment of stereochemistry, and the stereochemistry at the C-6 position was lost in the subsequent oxidation step.

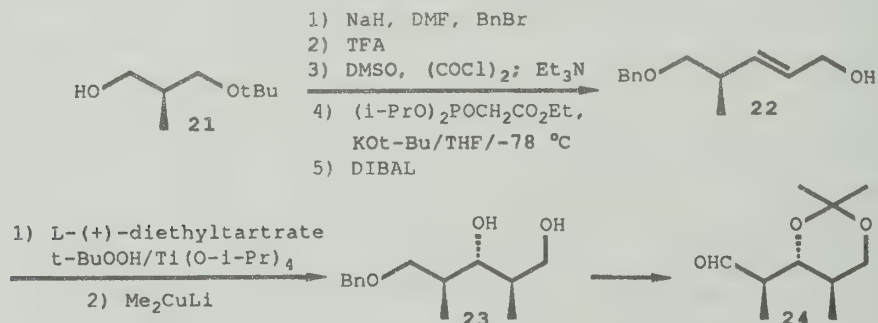




### 2,4-Dimethyl-1,3-Alkanediol Systems

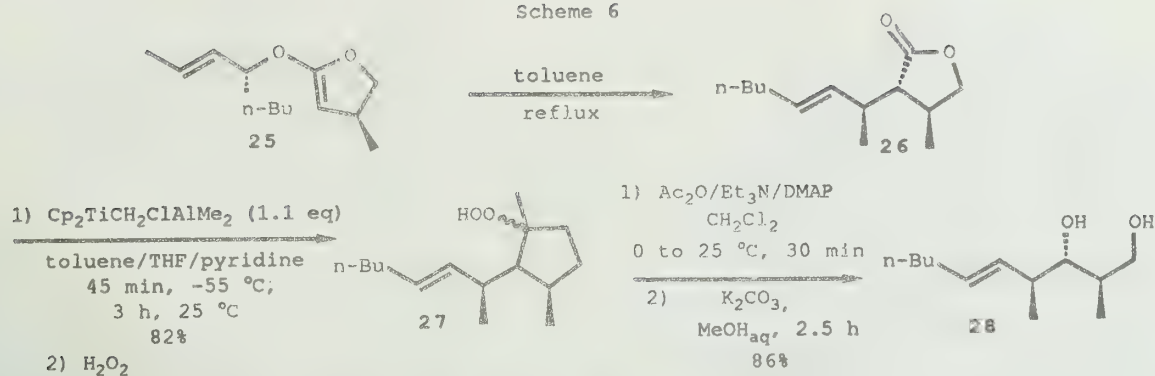
An aldehyde precursor to the 2,4-dimethyl-1,3-alkanediol system **8**, which contains three of the key stereocenters, has been synthesized by two different routes. The "Kishi aldehyde" **24** was synthesized starting from the chiral alcohol **21** (Scheme 5), which contains one of the asymmetric centers.<sup>20</sup> A two carbon homologation, done with a phosphonate reagent, gave the allylic alcohol **22**. Sharpless epoxidation followed by ring opening of the epoxide with dimethyl cuprate introduced two more stereocenters. The resulting diol **23** is then transformed into the Kishi aldehyde **24** in three routine steps.

Scheme 5



Ziegler's approach to the Kishi aldehyde utilized chiral compounds which already contained two of the asymmetric centers.<sup>21</sup> Condensation of S-3-methylbutyrolactone (as its diethoxy ortholactone) with R-(E)-2-octen-4-ol, followed by Claisen rearrangement of the adduct **25**, gave the lactone **26** (Scheme 6). Reaction of the lactone **26** with Tebbe's reagent followed by treatment with  $\text{H}_2\text{O}_2$  gave the hydroperoxides **27**. Criegee rearrangement of the acylated hydroperoxides gave a mixture of hydroxy acetates which provided the diol **28** after saponification. The Kishi aldehyde was then formed in two standard steps.

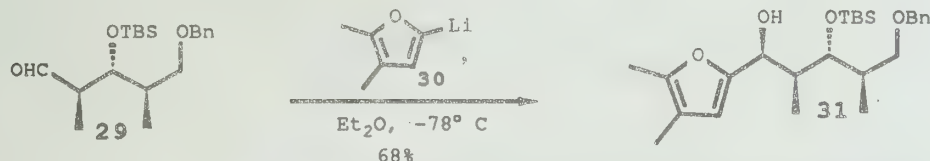
Scheme 6



### Enedione Approaches with the Kishi Aldehyde

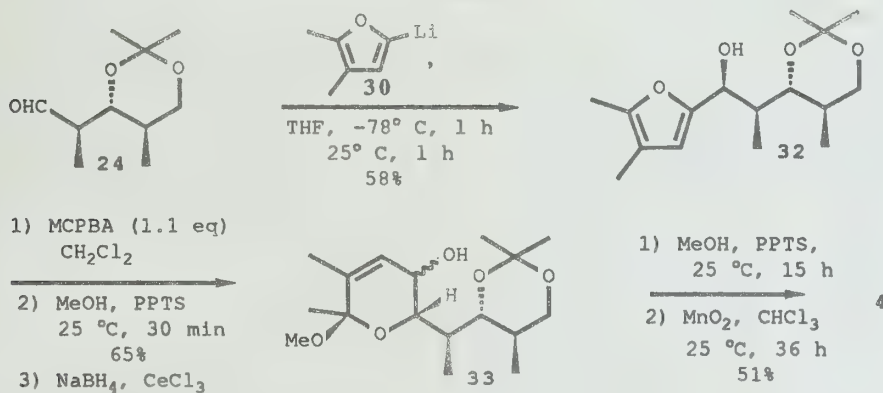
DeShong used an equivalent of the Kishi aldehyde in his synthesis. Coupling of the aldehyde **29** with the 2,3-dimethylfuran anion **30** gave a 1:1 mixture of adducts (Scheme 7). Some of the undesired diastereomer could be converted to the desired diastereomer **31** by  $\text{BaMnO}_4$  oxidation followed by stereoselective chelation controlled-reduction (1:1.7) with  $\text{Zn}(\text{BH}_4)_2$ . By this approach, the desired isomer **31** was obtained in a combined yield of 68%.

Scheme 7

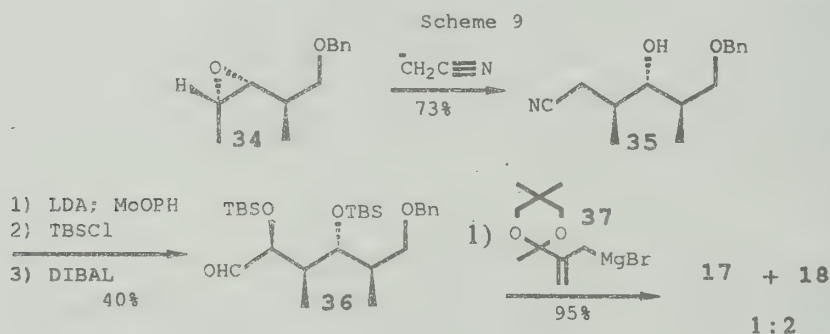


Ziegler found a higher stereoselection in the addition of **30** to the Kishi aldehyde (Scheme 8), obtaining the desired syn alcohol **32** in 58% yield (syn:anti = 1.7:1). Oxidation of the furan with MCPBA gave a mixture of anomeric dihydropyranones. Hydrolysis of the acetonide produced none of the desired bicyclic ketal. Ziegler circumvented this problem by forming a methoxyketal from the hemiketal. Reduction of the enone subunit gave the enol **33** (as a mixture of epimeric alcohols), which cyclized in the desired mode to a bicyclic ketal. Oxidation of this mixture gave Ireland's alcohol **4**.

Scheme 8

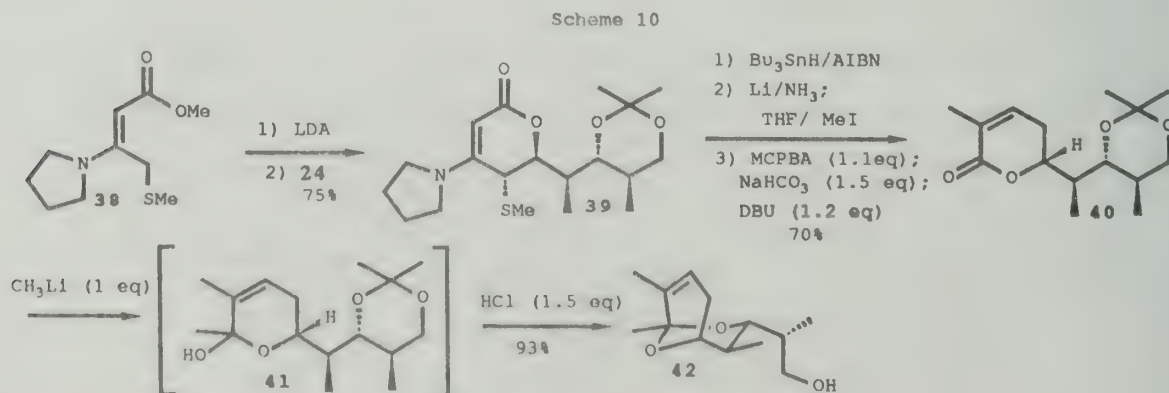


Kelly opened the epoxide **34** with the anion of acetonitrile to form **35** (Scheme 9), which contained the same three stereocenters as the Kishi aldehyde. Stereoselective hydroxylation proceeded to give the desired epimer in 45% yield (desired:undesired = 1.5:1). Protection of the free hydroxyl groups as the TBS ethers followed by DIBAL reduction afforded the aldehyde **36**. Coupling of the aldehyde **36** with the Grignard reagent **37** gave a 1:2 mixture of epimers. The TBS protecting groups of the mixture of epimers were removed. Deprotection of the acetonide with *p*-TsOH also effected closure to the bicyclic ketal. Only the minor epimer **17** could be converted to a bicyclic ketal (Eq. 4). The major epimer **18** cyclized in an alternative mode (Eq.5).



#### Other Approaches with the Kishi Aldehyde

Schlessinger<sup>22</sup> solved the problem of the stereoselectivity of the addition of the latent 1,4-enedione fragment to the Kishi aldehyde. The vinylogous urethane **38** was deprotonated and condensed with the Kishi aldehyde, providing the lactone **39** (Scheme 10). The thiomethyl group is the source of the high three stereoselection. Desulfurization and reductive methylation was followed by removal of the pyrrolidine residue, providing the lactone **40**. Reaction of the lactone **40** with MeLi gave an intermediate hemiketal **42** which was cyclized to the bicyclic ketal **42** with HCl in THF in 93% yield from the lactone **41**.

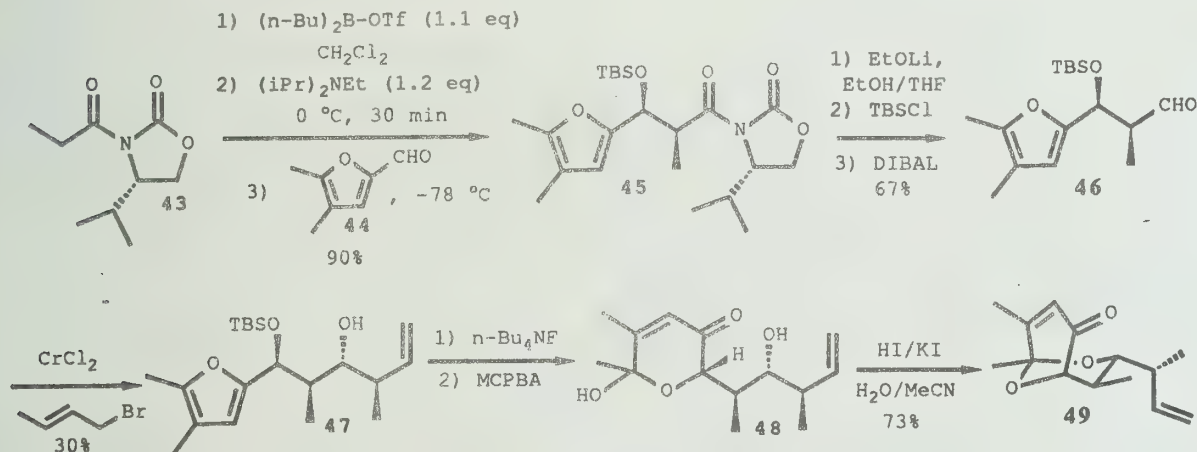




### Other Ene-Dione Approaches

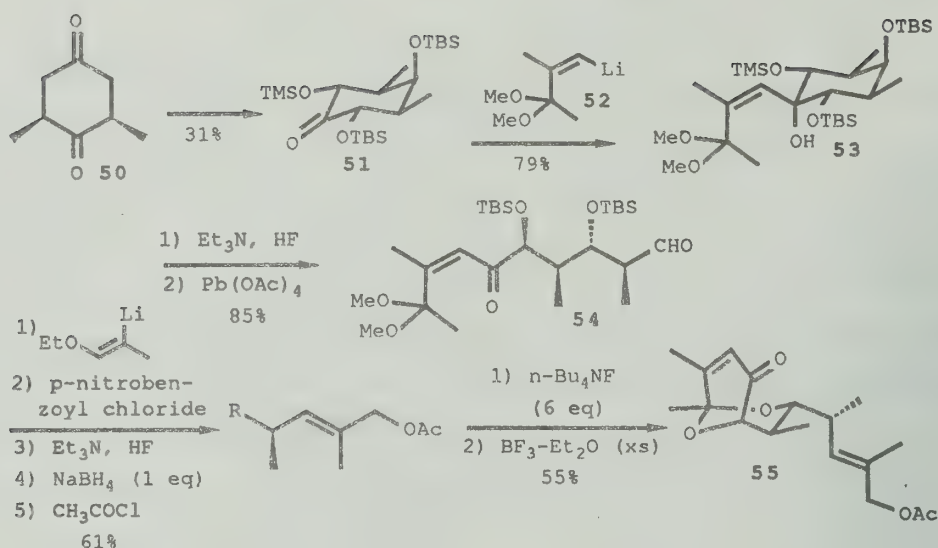
Martin<sup>23</sup> also used a furan precursor, but with different bond connections. Condensation of 4,5-dimethylfurfuraldehyde **43** with the boron enolate derived from the chiral oxazolidinone **44** (Scheme 11) gave the erythro adduct **45** in good diastereomeric excess (erythro:threo = 50:1). This was converted to the aldehyde **46** in 80-85% overall yield. The elaboration of the remaining two stereocenters, however, proceeded without significant stereoselectivity. The aldehyde **46** was treated with crotyl bromide in the presence of  $\text{CrCl}_2$ . The desired homoallylic alcohol **47** was obtained in 30% yield (desired:undesired = 1:1.5). Deprotection of the TBS ether and MCPBA oxidation of the furan provided the hemiketal **48**, which was cyclized to the bicyclic ketal **49** in 77% yield from the furan.

Scheme 11



Boeckman also used an enedione approach, based on the addition of a  $\beta$ -acyl vinyl anion equivalent to a cyclic carbonyl compound which has the four key stereocenters in place. The readily available 2,6-dimethyl-1,4-cyclohexanedione **50**, which contains a symmetry element that Boeckman recognized in the bicyclic ring system, was converted to ketone **51** (Scheme 12). Addition of the  $\beta$ -acyl vinyl anion equivalent **52** afforded the adduct **53**. Cleavage of the TMS group of **53** followed by fragmentation of the resulting diol with  $\text{Pb}(\text{OAc})_4$  led to the acyclic keto aldehyde **54**. Homologation of the aldehyde was followed by cleavage of the TBS ether protecting groups. One-step cyclization to the bicyclic ketal **55** occurred upon treatment with  $\text{BF}_3\text{-Et}_2\text{O}$ .

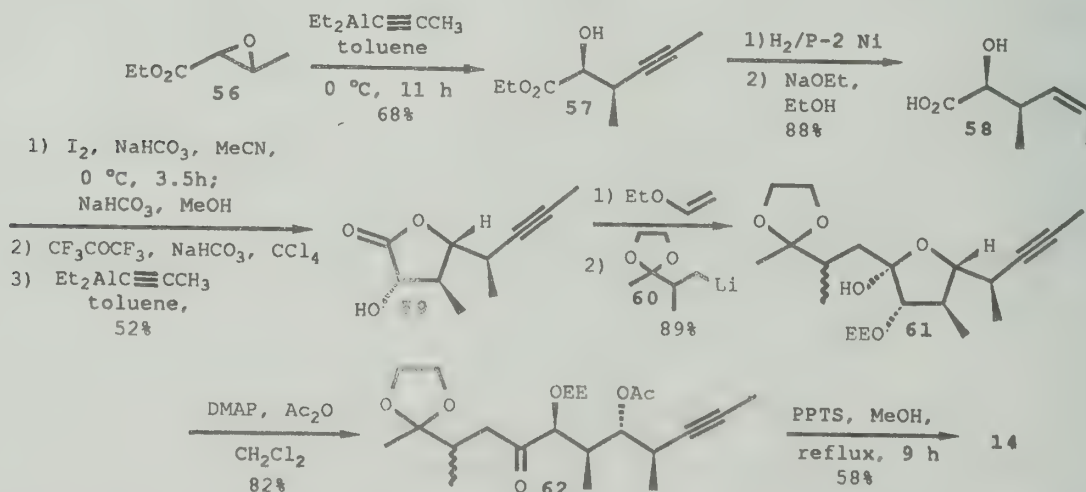
Scheme 12



### Other Approaches

Bartlett established the relative stereochemistry of the four contiguous stereocenters in the bicyclic ketal precursor by a sequence of epoxide formation and displacement reactions. Reaction of ethyl  $\alpha,\beta$ -epoxybutyrate **56** with diethylpropynylalane was followed by reduction of the alkyne **57** to a cis-alkene **58** (Scheme 13). This alkene was stereospecifically epoxidized by iodolactonization followed by methanolysis (20:1 ratio of isomers). The epoxid

Scheme 13

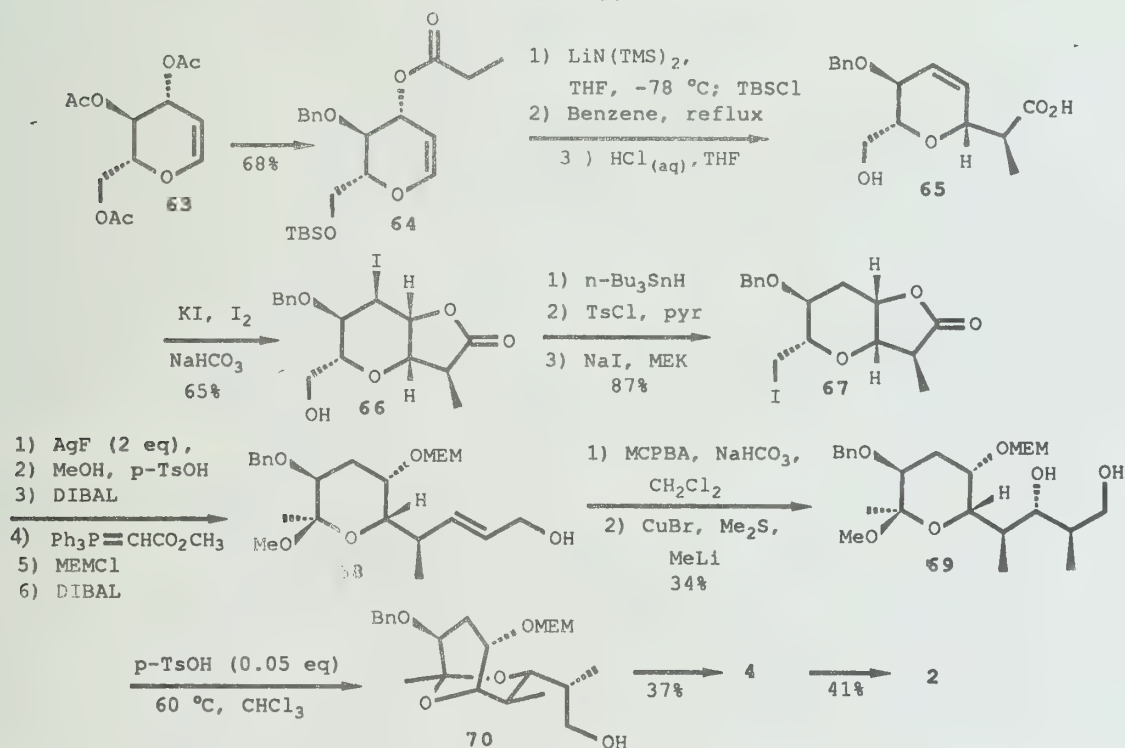


was opened stereospecifically in a two-step process to give an  $\alpha,\gamma$ -dihydroxy acid which cyclized to a  $\gamma$ -lactone **59**. The lithio ketal **60**, used as saturated equivalent of a  $\beta$ -acyl vinyl anion, added to the lactone **59** to give the hemiketal **61**, which was converted to the acyclic ketone **62** by acetylation. Formation of the bicyclic ketal was performed in a stepwise process through sequential release

of the hydroxyl groups. The ethoxyethyl (EE) group was removed with pyridinium p-toluenesulfonate (PPTS) in methanol, with cyclization to the tetrahydropyranone **14** occurring in 58% yield under these conditions. The minor isomer, in which the methyl group adjacent to the ketal was  $\alpha$ , formed in 24% yield. This isomer, after being reduced to an alcohol **16**, cyclized in an alternate mode upon exposure to acid (Eq. 3). The ketone group of the tetrahydropyranone **14** was reduced to an alcohol **15** with mainly a  $\beta$ -OH (6:1 mixture of isomers). This mixture undergoes cyclization with PPTS in  $\text{CHCl}_3$  to form the bicyclic[3.3.1]ketal (Eq. 2), in which the methyl group has undergone inversion, in 76% overall yield from the tetrahydropyranone **14**.

The first total synthesis of tyrandamycic acid in its optically active, natural form, was accomplished by Ireland<sup>24</sup> starting from D-glucose. The glycal **63**, obtained from D-glucose in two steps, was converted to the propionate **64** (Scheme 14). Two of the stereocenters are established in the Claisen rearrangement of the Z-enolate of the ester, which gave the C-glycoside **65** as a

Scheme 14



mixture of side-chain epimers (81:19). The major isomer was separated in the next step by crystallization of the iodolactone **66**. Alteration of the oxidation state at C5 was accomplished by conversion to the alternate iodolactone **67**, elimination

of HI, and addition of MeOH. Homologation of the carboxyl functions and reduction to the allylic alcohol 68 followed standard procedures. Epoxidation in the desired sense (10:1) was accomplished by MCPBA oxidation of the pyran 68. Dimethyl cuprate cleavage established the two remaining key stereocenters of 68. Cyclization to the bicyclic ketal 70 was accomplished with pTsOH in CHCl<sub>3</sub>. The functionality of this ketal was adjusted to that of the Ireland alcohol 4.

### Summary

In some of the approaches in which the Kishi aldehyde was used, the overall yield was low and it was necessary to separate, by HPLC, diastereomers which resulted from addition reactions of poor stereoselectivity. Schlessinger solved the problem with stereoselectivity, synthesizing tyrandamycin A in optically active form in 22% overall yield from the Kishi aldehyde. Bartlett also obtained good stereoselectivity, but his synthesis was long. Ireland utilized the natural chirality of D-glucose in his synthesis, obtaining tyrandamycin acid in 2% overall yield from D-glucose.

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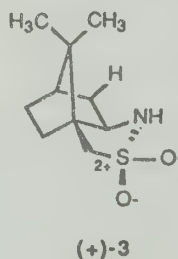
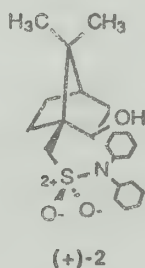
**10-DICYCLOHEXYLSULFAMOYLISOBORNEOL AND 2,10-CAMPHORSULTAM: POWERFUL  
AUXILIARIES FOR ASYMMETRIC SYNTHESIS.**

Reported by David J. Allen

March 12, 1987

**Introduction.**

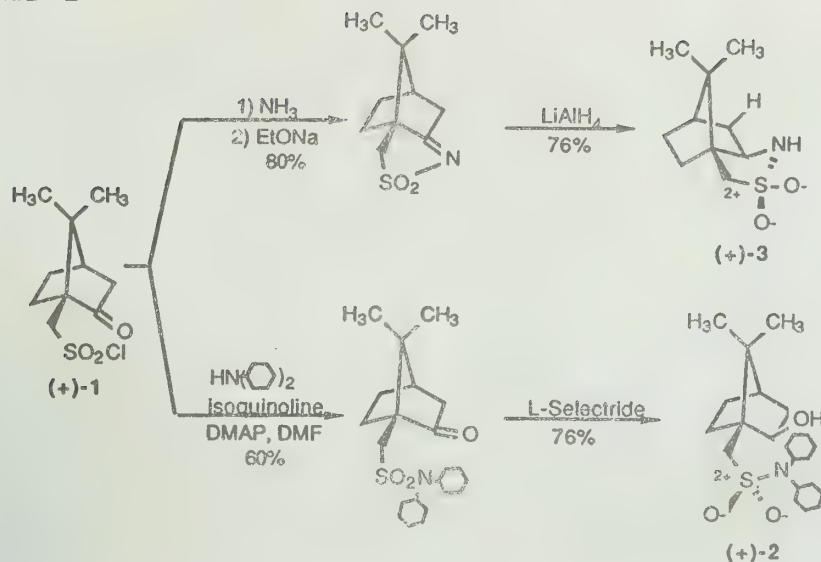
A great effort in the area of asymmetric synthesis has been expended on the development of versatile, efficient, and recoverable chiral auxiliaries which control the approach of a reagent in a specific direction. Encouraged by his early successes with the use of *cis*-2-diphenylmethoxy isoborneol and *cis*-2-neopentyloxy isoborneol in shielding one face of a  $\pi$ -system towards attack by a dieneophile in the Diels-Alder reaction,<sup>1</sup> Oppolzer has attempted to develop a versatile class of chiral auxiliaries which are highly crystalline, easily and quantitatively recoverable, and highly effective in shielding one face of a double bonded system in a variety of reactions. These attributes are present in two auxiliaries available in two steps from (+) or (-)-camphor-10-sulfonyl chloride: 10-dicyclohexylsulfamoylisoborneol (2) and 2,10-camphor-sultam (3).



**Synthesis of Chiral Auxiliaries.**

The chiral auxiliaries were both prepared from readily available optically active camphor-10-sulfonyl chloride (1) in 2 steps (Scheme 1). Amidation of 1 using dicyclohexylamine followed by selective reduction of the ketone with *L*-selectride gave after one crystallization a 55% overall yield of (+)-10-dicyclohexylsulfamoylisoborneol with greater than 99% optical purity.<sup>2</sup> The (+)-sultam was made via amidation of the chloride with  $\text{NH}_3$ , followed by base induced cyclization to give the imine in 80% yield. Selective reduction of the imine with  $\text{LiAlH}_4$  gave the optically pure sultam in 61% overall yield. Both antipodal forms are available in two steps and in good yield from (+) or (-)-camphor-10-sulfonyl chloride.<sup>3</sup>

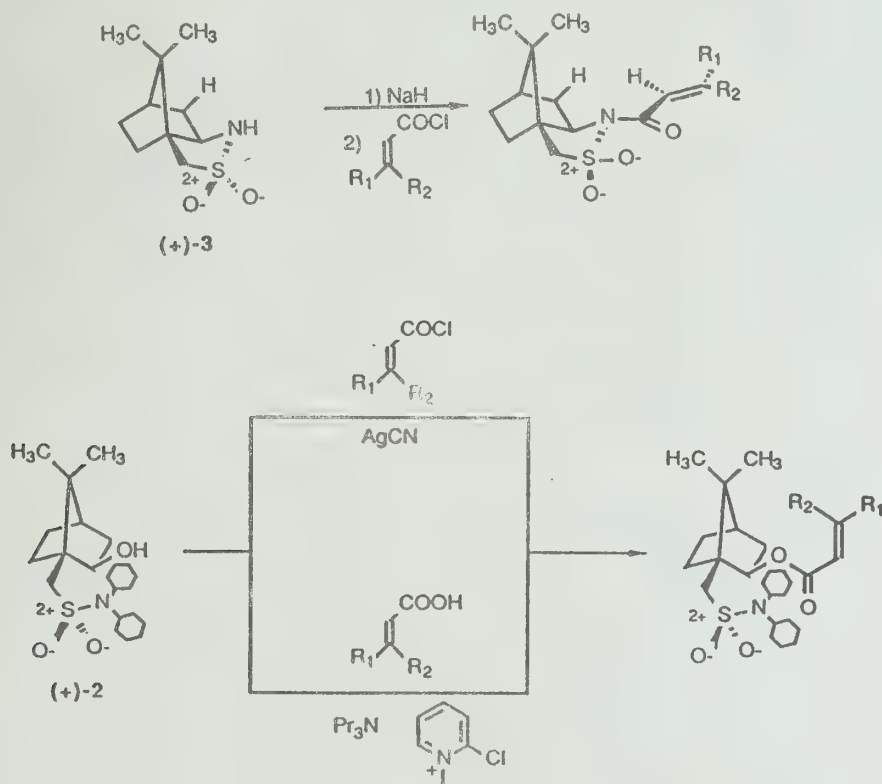
Scheme 1



### Preparation of Derivatives of the Chiral Auxiliaries.

Systems to undergo stereoselective reaction are attached to the auxiliaries via N or O acylation (Scheme 2). The camphor sultam derivatives are prepared by deprotonation of the auxiliary followed by the addition of the desired acid chloride, to yield the imides in 50-88 percent yield after crystallization.<sup>3</sup> Esterification of the sulfonamide auxiliary is achieved by a variety of methods. Treatment of the auxiliary alcohol with an acid chloride in the presence of  $\text{AgCN}$  gives the ester in 82-94 percent yield; reaction of the alcohol with acrylic acid, tripropylamine, and N-methyl- $\alpha$ -chloropyridinium iodide in refluxing toluene yields the crystalline ester in 87-92 percent yield.<sup>2</sup>

Scheme 2



## Diastereomeric Separations and Recoveries of Chiral Auxiliaries.

Since most asymmetric inductions are not 100% selective, a major issue concerns the separability of diastereomeric products. The camphorsulfonyl derived chiral auxiliaries of Oppolzer have the advantage of being highly crystalline, so that the separation of diastereomeric products can often be achieved efficiently by crystallization, giving, ultimately, products with very high diastereomeric or enantiomeric excess (de or ee).

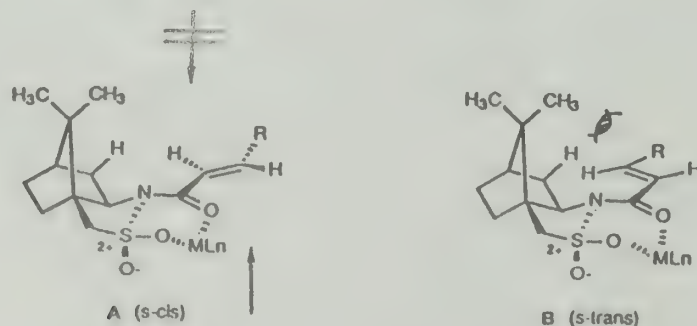
Once the reaction of interest is complete and the diastereomeric mixture purified, the auxiliaries can be easily and non-destructively removed, leaving the substrate at either the alcohol or acid oxidation state.<sup>4</sup> Saponification of the adduct with LiOH in aqueous THF, or treatment with methanolic  $K_2CO_3$ , liberates the enantiomerically pure acid in nearly quantitative yield, the crystalline auxiliary being recovered generally in greater than 90 percent yield. To cleave the auxiliary and reduce the amide substrate to an alcohol,  $LiAlH_4$  or  $Ca(BH_4)_2$  is added and the sulfonamide or sultam was separated from the alcohol by crystallization. Recoveries of both components are generally in the 93-99 percent range.

## Mechanism Of Selectivity

### Additions to $\alpha\beta$ -Unsaturated Carbonyl Systems.

The selectivity in this use of these chiral auxiliaries stems from the blocking of one face of the alkene by the chiral auxiliary. With the camphorsultam, the shielding comes from the gem-dimethyl group on the single carbon bridge of the camphor skeleton. Through conjugation with the nitrogen lone pair, the enone lies approximately planar to the camphor skeleton base, and complexation with a Lewis acid locks the carbonyl and sulfone oxygens in a syn orientation. The planar unsaturated system can either adapt an s-cis or s-trans conformation, as shown, with the s-cis conformation (A) being favored over the s-trans conformation (B) due to steric hinderance between the vinyl hydrogen and the hydrogens on C-3. Assuming the transition state energies mirror that of the ground state, approach of the substrate, either a Diels-Alder diene or an organocopper reagent, is then blocked by the endo methyl group attached to C-7.<sup>3, 5</sup> This conformation blocks the si-si face of the olefin, leaving the re-re face open to attack (Scheme 3).

Scheme 3

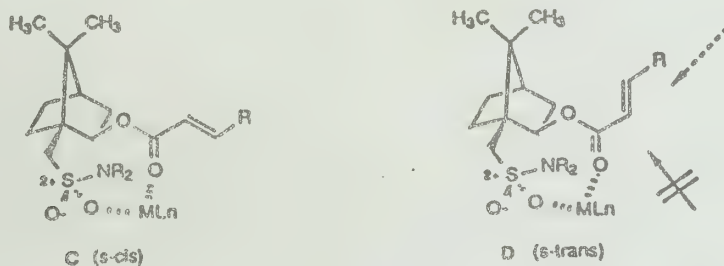




With regard to asymmetric hydrogenations of the enoyl derivatives of the sultam, selectivity comes from the complexation of the auxilliary to the metal on the less hindered side, with delivery of the hydrogen from the metal surface to the same side.<sup>6</sup>

The sulfonamide employs the cyclohexyl rings to block the approach from one side of the molecule. Again, the carbonyl and sulfone oxygens are brought into close proximity by complexation to a Lewis acid. The planar,  $\alpha,\beta$ -unsaturated system orients itself in the H-C(2)-O plane to avoid steric interaction with the amide functionality. Thus, the competing conformations in the transition state become the s-cis and the s-trans forms of the enone system, with the s-trans favored in this case. This blocks the re-re face of the olefin, directing addition selectively to the si-si face (Scheme 4).<sup>5a</sup>

Scheme 4



#### Additions to Enolate Systems.

In addition to the blocking of one side of the double bond system, the enolate geometry must be specifically defined in order for enolate additions to proceed stereoselectively. By employing a bulky base such as lithium diisopropylamide, the Z-enolate is formed specifically. This is consistent with the Ireland transition state model for  $\alpha$ -deprotonation, which predicts approach of the base away from the more bulky group  $\alpha$  to the carbonyl (Scheme 5). Once formed, one face of the enolate is blocked in a fashion analogous to the  $\alpha,\beta$ -unsaturated systems.<sup>2b, 4</sup>

Scheme 5



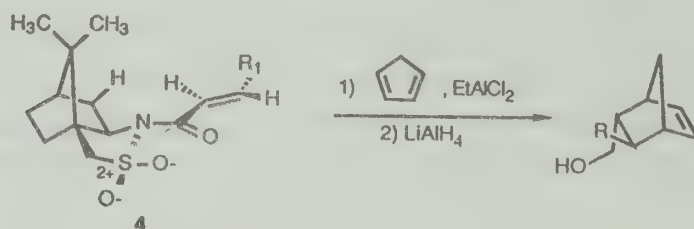
## Applications of Chiral Auxiliaries in Stereoselective Synthesis:

### Diels-Alder Reactions.

The auxiliary which has seen the most applications in the Diels-Alder reaction is the camphorsultam derivative. Oppolzer has studied the reaction of N-acroyl and N-crotonoyl derivatives to cyclopentadiene and the less reactive butadiene under Lewis acid catalyzed conditions, finding excellent diastereomeric selectivities in most cases (see Table 1). In all cases, the optical purity could be raised to greater than 99 percent via crystallization. Oppolzer's data shows that selectivity is increased by utilizing stronger Lewis acids and 1.5 equivalents rather than 0.5 equivalents Lewis acid. High endo selectivity predominates in all cases.<sup>2a,3,5b</sup> The topicity of the addition was easily reversed via utilization of the antipodal auxiliary.

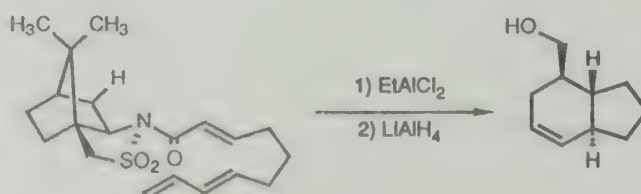
Table 1: Additions of dienes to 2,10-camphorsultam derived dieneophiles (4)

Dieneophile	Lewis Acid	Temp (°C)	ee alcohol (%)	
			0.5 eq Lewis acid	1.5 eq Lewis acid
acrylate (R=H)	EtAlCl <sub>2</sub>	-130	85	95
	TiCl <sub>4</sub>	-130	91	94
	Et <sub>2</sub> AlCl	-130	65	93
	SnCl <sub>4</sub>	-130	90	91
	BF <sub>3</sub> ·OEt <sub>2</sub>	-130	NR	51
crotonate (R=CH <sub>3</sub> )	EtAlCl <sub>2</sub>	-78	—	98
	TiCl <sub>4</sub>	-78	93	—
	BF <sub>3</sub> ·OEt <sub>2</sub>	-78	—	NR



Oppolzer has applied the face shielding of the camphorsultam to an intramolecular Diels-Alder reaction. Treatment of a triene derived camphorsultam with EtAlCl<sub>2</sub>, gave the Diels-Alder adduct in greater than 94.5 percent diastereomeric excess, which was increased to greater than 99 % de by crystallization (Scheme 6).

Scheme 6



Many other methods exist for obtaining enantioselectivity in the Diels-Alder reaction by utilizing chiral dieneophiles; Several of these are capable of achieving selectivities of >90%.<sup>7a,b</sup> A few of the more popular methods include the use of optically active oxazolidinone derivatives,<sup>7c</sup> and optically active  $\alpha$ -hydroxy ketones.<sup>7d</sup> However, aside from the camphor sultam, few examples of highly enantioselective intramolecular Diels-Alder reactions exist.<sup>7c,e,f</sup>

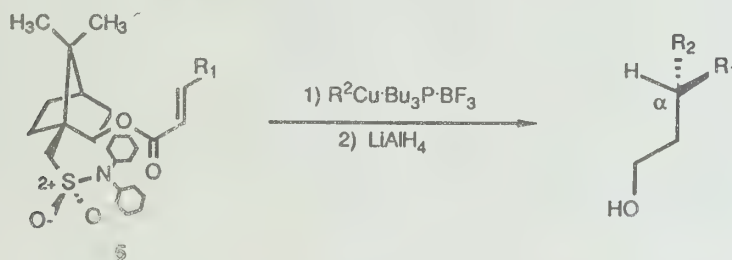
### Conjugate Additions.

Oppolzer has applied the sulfonamide auxiliary to achieve asymmetric conjugate additions to a variety of  $\alpha,\beta$ -unsaturated amide systems. Addition of alkyl copper- $\text{BF}_3$  complexes yielded 80-98 percent of the addition adduct, and saponification of the amide gave the  $\beta$ -substituted carboxylic acids in 94-98% ee (See table 2).<sup>4a,5a</sup> The sense of induction of the  $\beta$ -carbon is easily reversed by either reversing  $\text{R}^1$  and  $\text{R}^2$ , or by using the antipodal auxiliary.<sup>4a</sup>

Isoborneolsulfonamide derivatives developed by Helmchen give similar selectivities on addition of  $\text{RCu} \cdot \text{BF}_3$ .<sup>8a</sup> Other methods of asymmetric conjugate additions involve chiral vinyl sulfoximines<sup>8b,c,d</sup> and aldimines.<sup>8e</sup>

Table 2: Addition of  $\text{RCu} \cdot \text{Bu}_3\text{P} \cdot \text{BF}_3$  to chiral camphorsultam derivatives (5)

$\text{R}^1$	$\text{R}^2$	yield (%)	ee (%)	configuration at $\text{C}_\alpha$
Me	Pr	99	97	R
Me	Bu	89	97	R
Me	Vinyl	80	98	S
Me	2-propenyl	84	94	R
Pr	Me	89	94	S
Bu	Me	93	97	S



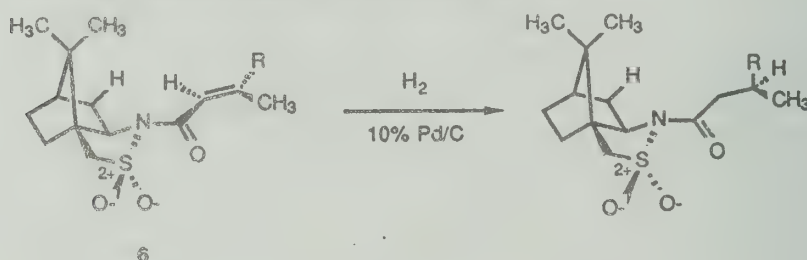
### Hydrogenations.

Because of the high enantioselectivity of the Diels-Alder and conjugate addition reactions of  $\alpha,\beta$ -unsaturated carbonyl systems, Oppolzer attempted to extend the usefulness of the camphorsultam auxiliary to asymmetric hydrogenations.<sup>6</sup> Catalytic hydrogenation over 10% Pd black at 95 Psi proceeded smoothly, with the de's of various reductions ranging from 90-97%. These could be increased to greater than 99.5 % de upon crystallization (Table 3). Again, the

opposite enantiomer could be obtained by reversing the olefin geometry or employing the (-) auxiliary.

Table 3: Asymmetric hydrogenations of chiral camphorsultam derivatives (6)

R	yield (%)	de (%)	
		crude	recrystallized
Et	99	—	>99
n-Pr	95	96	
i-Pr	97	91	
Bu	95	90	
n-Hexyl	99	92	
n-Octyl	93	—	>99



A multitude of examples of homogeneous asymmetric hydrogenations via chiral rhodium or indium catalysts exist.<sup>9</sup> However, this method represents a rare example of heterogeneous catalytic hydrogenation yielding optically active products.

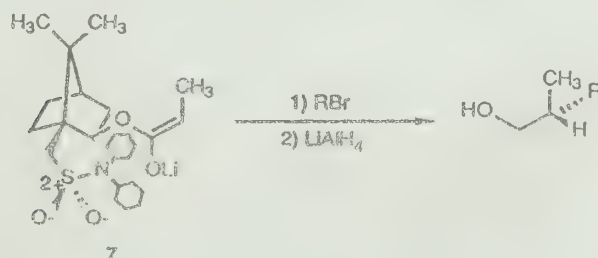
#### Enolate alkylation.

The area in which 10-dicyclohexyl- sulfamoylisoborneol has found the most utility is in controlling the stereochemistry of additions to enolates. Kinetically-controlled deprotonation with lithium diisopropylamide of the ester yields the Z-enolate, in which the C<sub>a</sub>-re face is blocked by the cyclohexyl ring surface. Subsequent addition of alkyl bromides, even the unactivated propyl bromide, results in α-alkylated esters in 78-98% de.<sup>4a</sup> The diastereomeric excess can be increased by means of a simple crystallization (as illustrated in Table 4, first entry) and the optically active alcohol is obtained by reduction in 92-100% yield, with recovery of the crystalline auxiliary in 88-96% yield.



Table 4: Alkylations of chiral sufamoylisoborneol derivatives ( 7 )

R	yield (%)	ee (%) of alcohol	crystallized yield (%)	crystallized ee (%)
benzyl	84	89	61	98
allyl	94	88		
propyl	92	78		

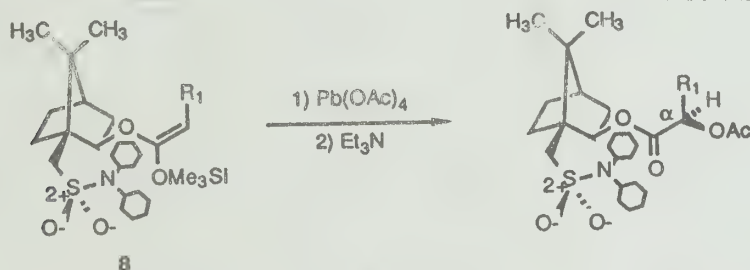


Other examples of asymmetric alkylations via chiral directing groups include Meyers' oxazolines, Evans' oxazolidinones, and Enders' hydrazones, all of which have seen success similar to Oppolzer's sulfonamides.<sup>10</sup>

**Enolate  $\alpha$ -Acetoxylation.** Oppolzer has obtained highly enantioselective  $\alpha$ -acetoxylation of the enolate sulfonamide derivative.<sup>4b</sup> Treatment of the Z-enolate with  $\text{Pb}(\text{OAc})_4$  followed by saponification, gave the  $\alpha$ -hydroxy acid in 88-99% ee, which could be increased by crystallization prior to saponification (Table 5). The configuration of the  $\alpha$  carbon could be reversed by utilizing the antipodal auxiliary. The addition appears in these examples to occur to the most hindered face. This can be rationalized by attack of the electrophilic metal on the less hindered face of the enolate, with opening of the leadonium ion with acetate ion by inversion.

Table 5:  $\alpha$  -Acetoxylation of chiral sufamoylisoborneol derivatives ( 8 )

Auxiliary	R	crude de (%)	crystallized de (%)	configuration at $C_\alpha$
(+)-2	n-Bu	90.5	95	R
(-)-2	n-Octyl	96	98.6	S



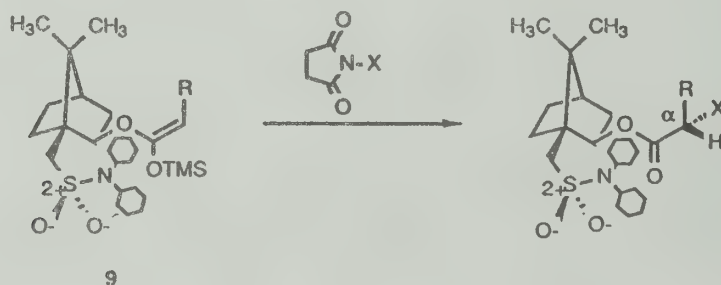
Other enantioselective preparations of  $\alpha$ -hydroxy or  $\alpha$ -acetoxy acids or diols by enolates include additions to oxazolidinones via oxaziridines<sup>11a</sup> and to chiral esters via  $\text{MoO}_5$  complexes.<sup>11b</sup>

### Enolate halogenation.

A more recent application of the sulfonamide auxiliary involves electrophilic  $\alpha$ -brominations.<sup>2b</sup> The ester is selectively deprotonated to form the Z-enolate, which selectively adds "Hal<sup>+</sup>", via NBS or NCS, to the C $_{\alpha}$ -si face. This addition proceeds in 76-96% de, which can be increased to greater than 96% de by crystallization (Table 6). The optically active alkyl halides can be reduced to the halohydrin with LiAlH<sub>4</sub>, from which optically active terminal epoxides can be prepared in greater than 90% ee. Oppolzer was able to extend this work to the synthesis of natural and unnatural amino acids.<sup>12</sup> Few other examples of asymmetric  $\alpha$ -halogenations of enolates exist.

Table 6: Asymmetric  $\alpha$ -Halogenation of chiral sulfamoylisoborneol derivatives (9)

Auxiliary	R	X	Crystallized yield (%)	Crystallized de (%)	Configuration at C $_{\alpha}$ .
(+)-2	Me	Cl	77	98	S
(+)-2	n-Bu	Br	68	>96	S
(+)-2	n-Bu	Cl	67	>96	S
(+)-2	Phenyl	Cl	54	>96	S
(+)-2	i-Amyl	Br	66	>96	S
(+)-2	n-Octyl	Cl	62	>99	S
(-)-2	n-Octyl	Br	68	>96	R



### Conclusion.

The chiral auxiliaries 2,10-camphorsultam and 10-dicyclohexylsulfamoylisoborneol have been shown to be effective chiral auxiliaries for asymmetric additions to  $\alpha,\beta$ -unsaturated carbonyls and enolate systems. Their availability, quantitative placement and recovery, their high crystallinity and effective face shielding ability make them useful for a wide variety of asymmetric reactions.

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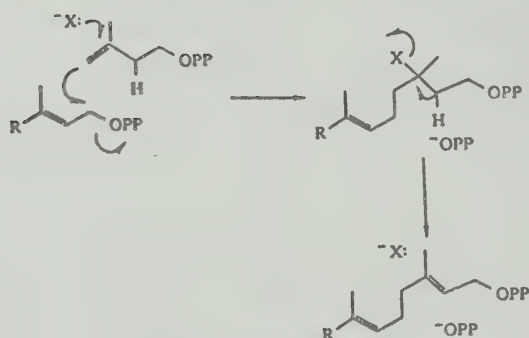
## THE MECHANISM OF PRENYL TRANSFER IN TERPENE BIOSYNTHESIS

Nelson T. Rotto

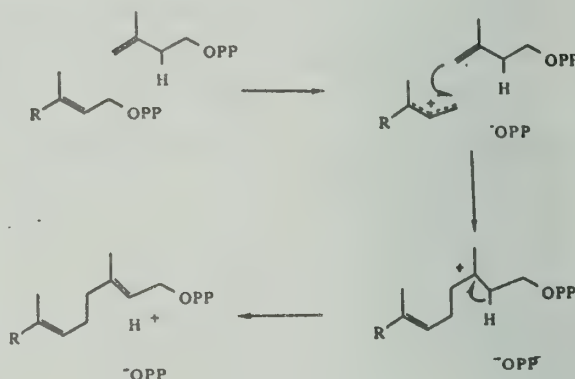
Thursday, April 2, 1987

The pioneering work of Cornforth and Popjack<sup>1</sup> on cholesterol biosynthesis resulted in the previously accepted "X - group" mechanism of prenyl transfer. This "X - group" mechanism was based largely on stereochemical evidence.

## "X - GROUP MECHANISM"



## "IONIZATION-CONDENSATION-ELIMINATION"



However, extensive kinetic studies by Poulter, Rilling and others with farnesyl pyrophosphate (PP) synthetase have led to the proposal of an ionization - condensation - elimination mechanism involving an ion pair between PP and allylic substrate.<sup>2</sup> Solvolysis experiments and enzyme incubations with fluorine substituted prenyl substrates support this  $S_N1$ -type mechanism.<sup>3</sup> The observation that inorganic PP stimulates hydrolysis of allylic substrates also provides evidence for the proposed mechanism.<sup>2b,4</sup> Linear free energy relationships suggest that the ionization process is unassisted by the double bond of isopentenyl PP and is a discrete step.<sup>5</sup> Oxygen-18 labeling experiments with  $[1-^{18}O]$  geranyl PP gave no scrambling indicating a tight allyl cation - PP anion pair (or the absence of ion pair return).<sup>6</sup> All experiments designed to reveal the proposed enzyme bound "X - group" were unsuccessful.<sup>8</sup> It should be noted that the involvement of allyl carbocation - PP ion pairs in terpene cyclases and isomerases is now well established.<sup>7</sup>



Divalent metal ( $Mg^{+2}$ ,  $Mn^{+2}$ ,  $Zn^{+2}$ ) is essential for enzyme catalysis with farnesyl PP synthetase but is not necessary for substrate binding.<sup>9</sup> Two metal cations are bound in each active site and function to initiate the catalytic sequence by assisting ionization of the allylic PP.<sup>9</sup> Isotope partitioning experiments strongly support an ordered mechanism of substrate binding with allylic PP binding before isopentenyl PP.<sup>10</sup>

The substrate specificity of farnesyl PP synthetase has been extensively studied by Ogura and co-workers by incubation of artificial allylic and homoallylic pyrophosphates. Studies have shown that the enzyme can tolerate moderate changes in allylic substrate but only minor changes in homoallylic substrate are accepted.<sup>11</sup>

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PROPOSED CHEMICAL APPROACHES TO THE IN VIVO DIAGNOSIS  
AND TREATMENT OF ALZHEIMER'S DEMENTIA

Reported by Marty Pomper

April 20, 1987

Clinically, Alzheimer's dementia (AD) presents as a progressive and inexorable loss of memory and cognitive function in elderly individuals.<sup>1</sup> Very recently, tremendous advances have been made toward understanding AD at the molecular and genetic levels.<sup>2</sup> Irrespective of these advances, the etiology of AD remains elusive, and no treatment or definitive in vivo diagnostic test exists.

Aluminosilicate toxicity,<sup>3</sup> disruption of the blood-brain barrier,<sup>4</sup> viral or subviral infection,<sup>5</sup> as well as aberrant neuronal metabolism or genetic control<sup>2</sup> have all been proffered as possible causes of AD. Momentarily ignoring etiology, while concentrating on what has been experimentally defined regarding AD, enables one to envision potential new modes of diagnosis and treatment. For instance, it is known that a profound decrease in the population of certain cholinergic neurons accompanies AD.<sup>6</sup> One possible explanation for the selective toxicity to cholinergic neurons is that an endogenous neurotransmitter, such as glutamic acid, may be causing their chronic over-stimulation. Such an "excitotoxic" mechanism for glutamate action has been well documented.<sup>7</sup> Supporting this hypothesis is the fact that a selective loss of cortical and hippocampal glutamate receptors has been demonstrated in AD.<sup>8</sup> Additionally, in vitro, glutamic acid has been shown to induce intraneuronal lesions resembling those seen in AD brain,<sup>9</sup> and glutamate levels in cerebrospinal fluid of AD patients have been found to be directly related to cognitive impairment.<sup>10</sup>

Positron emission tomography (PET)<sup>11</sup> could exploit a selective glutamate receptor deficit by producing an image which would be characteristic of AD patients. Of course, PET relies on the ready availability of suitable imaging agents, i.e., glutamate and its analogues incorporated with a positron-emitting radionuclide, e.g., <sup>18</sup>F. Four distinct subtypes of glutamate receptors have been identified in brain tissue,<sup>12</sup> and <sup>18</sup>F-labeled compounds which could selectively bind each would be valuable tools for investigating specific receptor deficits in AD.

Treatment of AD could consist of pharmacological manipulation of the glutamatergic synapse, directed toward limiting the availability of neurotransmitter glutamate.<sup>7</sup> A compound which inhibits release of glutamate presynaptically exists, and has already entered clinical trials for treatment of Huntington's chorea, another progressive neurological disorder believed to have an excitotoxic component.<sup>13</sup> Inhibition of the

primary biosynthetic enzyme of neurotransmitter glutamate, phosphate-activated glutaminase (PAG), could present a new approach to treatment of AD. Pursuing this possibility, potential active-site-directed, transition-state analogue and mechanism-based inhibitors can be designed,<sup>14</sup> all which are based on the glutamate skeleton.

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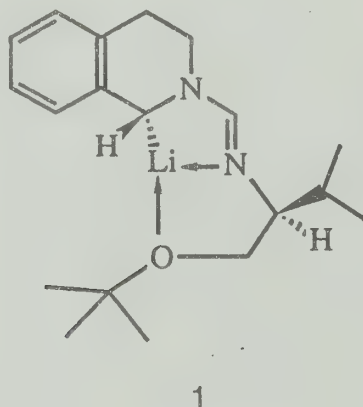
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STEREOGENIC  $\alpha$ -HETEROATOM ALKYL CARBANIONS

Reported by Roberta L. Dorow

April 23, 1987

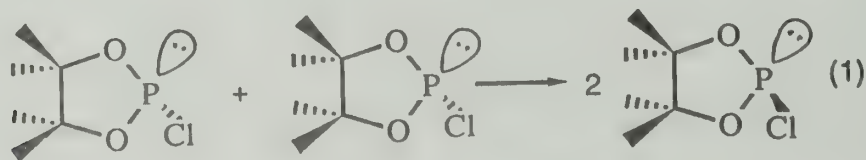
Stereogenic  $\alpha$ -heteroatom alkyl carbanions are assuming increasing importance in organic chemistry as evidenced by the work of Meyers on chiral formamidine anions 1,<sup>1</sup> which are dipole-stabilized carbanions. The subject of dipole stabilization has been reviewed by Beak<sup>2</sup> and will not be discussed here. However, the use and stabilization of other stereogenic  $\alpha$ -heteroatom carbanions will be considered.



## MECHANISMS OF RACEMIZATION

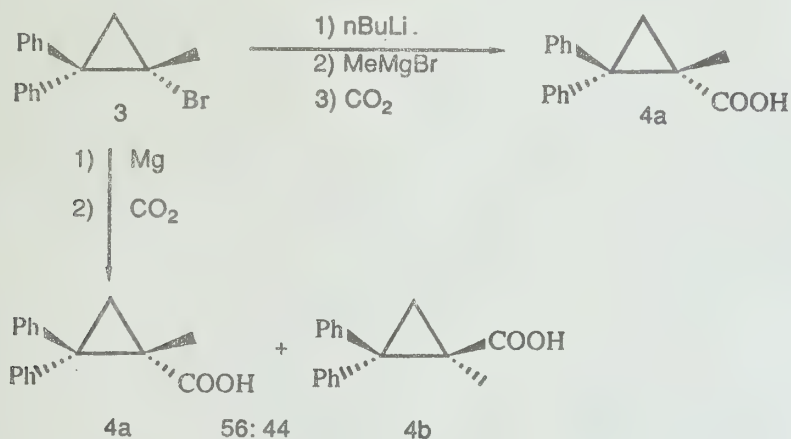
**Pyramidal Inversion** - In order to be synthetically useful, alkyl stereogenic carbanions must be configurationally stable. One racemization mechanism is pyramidal inversion. The inversion barrier for methyl carbanion has been shown by calculation to be low, only 5.5 kcal/mol.<sup>3</sup> (Dimethyl amine, which is isoelectronic with methyl carbanion, has a higher inversion barrier of 8.6 kcal/mol.<sup>3</sup>) Thus, for these carbanions to be useful in asymmetric synthesis, ways must be found to increase the barrier to inversion so as to make them configurationally stable.

**Ligand Exchange** - Another  $\alpha$ -heteroatom carbanion racemization mechanism is ligand exchange. This is analogous to the observed phosphorus inversion in 2-chloro-1,3-dioxaphospholanes 2 which has been shown by <sup>1</sup>H NMR and dilution studies to occur by intermolecular chlorine transfer (eq 1).<sup>4</sup>





**Radical Formation** - The success in generating a stereogenic carbanion from optically active starting materials without racemization may depend on the method used to produce the carbanion. In direct metalation, radical species may intervene and undergo rapid inversion, so that the carbanion formed, though configurationally stable, may have been racemized during its formation. Thus, treatment of optically pure bromocyclopropane **3** with magnesium in THF followed by carbonation of the Grignard reagent gives the cyclopropyl carboxylic acids **4a,b** in 12% ee (Scheme I).<sup>5</sup> In order to show that racemization occurred during the formation of the Grignard reagent, the Grignard reagent was synthesized by transmetalation of the corresponding cyclopropyllithium (which was known to be configurationally stable and could be generated without racemization by metal-halogen exchange). Carbonation of this Grignard reagent gives cyclopropyl carboxylic acid **4a** with complete retention of configuration.



SCHEME I.

### STABILIZATION AGAINST PYRAMIDAL INVERSION

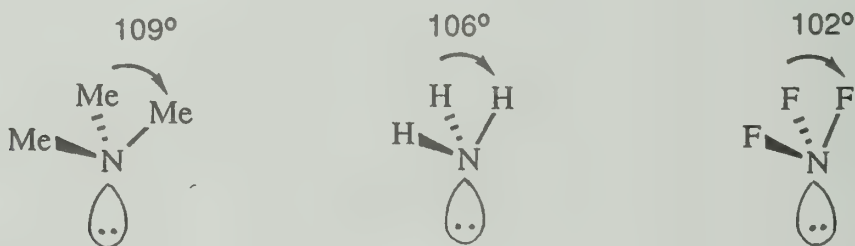
**Bond Angle and Electronegative Substituents** - Carbanions can be stabilized against pyramidal inversion by an  $\alpha$ -heteroatom substituent and by placement of the carbanionic center in a strained ring. An explanation of these effects has been provided in a review by Bent.<sup>6</sup> These effects are exemplified in the isoelectronic amine system by the increased activation energy of pyramidal inversion in nitrogen-substituted aziridines, as shown in Table I.<sup>3</sup>

TABLE I.  
N-SUBSTITUTED AZIRIDINE INVERSION BARRIERS

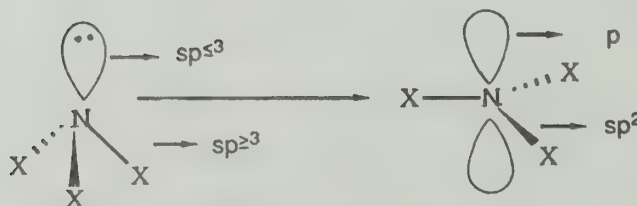


X	$E_a$ (kcal/mol)
Ph	14.6
H	21.3
Cl	33.4
F	49.5

Substituting electronegative groups on the aziridine nitrogen causes a rise in the inversion barrier. Bent accounts for this behavior by noting that s-character tends to concentrate in lone pair orbitals or, in other words, in orbitals to electropositive substituents. As the aziridine nitrogen substituent becomes more electronegative, there is an increase in the amount of s-character in the lone pair orbital and a decrease in the CNC bond angle (Scheme II). As the bond angle decreases, a greater bond distortion is required for the amine to achieve the planar transition state for inversion (Scheme III), and the inversion barrier is raised. In the process of inversion, the lone pair orbital goes from  $sp^3$  hybridization to pure p. Since the lone pair is s-character seeking, this also raises the inversion barrier.



SCHEME II.

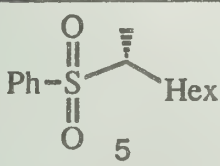
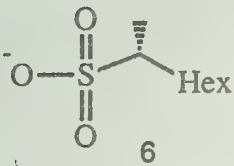
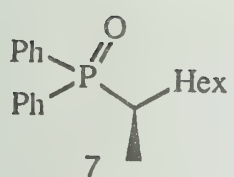
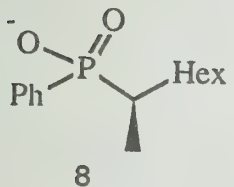


SCHEME III.

Comparison of the inversion barrier of dimethyl amine (8.6 kcal/mol) to that of aziridine shows a difference of 12.7 kcal/mol. This further illustrates the effect that increased bond distortion has on the inversion barrier.

**Electrostatic Repulsion** - The use of second row  $\alpha$ -heteroatoms to stabilize carbanions can involve factors other than electronegativity, for example, electrostatic repulsion. Cram examined the effect of various sulfur-based<sup>7,9</sup> and phosphorus-based<sup>8,9</sup> substituents on carbanion racemization (Table II), by measuring the ratio of rate constants for exchange and for racemization; a large ratio indicates a configurationally stable carbanion. As the table shows, only the phosphinic acid 8 and the sulfone 5 are reasonably stable.

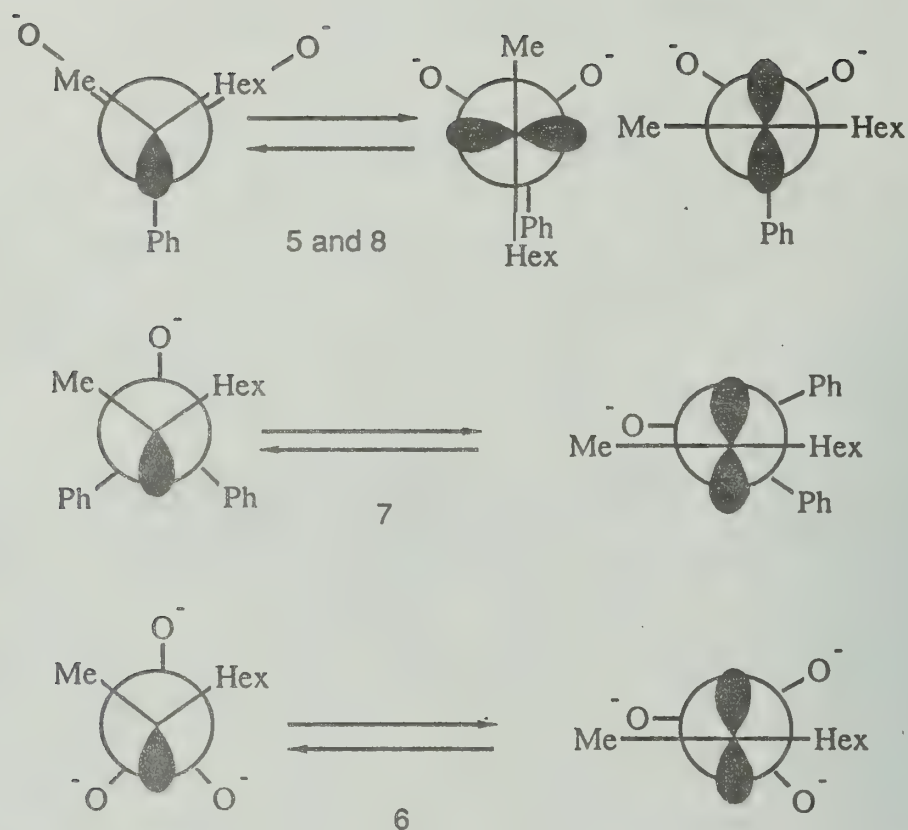
TABLE II.<sup>a</sup>  
CARBANION STABILITIES TO RACEMIZATION

COMPOUND	TEMP(°C)	TIME(hr)	$k_e/k_\alpha^b$
	25	0.3	129.0
	146	45.0	1.6
	100	11.5	3.3
	225	47.0	21.0

a) base/solvent =  $t\text{BuOK}/t\text{BuOD}$

b)  $k_e/k_\alpha = k_{\text{exchange}}/k_{\text{racemization}}$

Cram rationalizes these results in terms of the difference between electrostatic repulsion in the ground state tetrahedral carbanion and the trigonal carbanion in the transition state for inversion (Scheme IV).



SCHEME IV.

With the sulfone 5 and the phosphinic acid 8, there is a great increase in electrostatic repulsion in the transition state as compared to the ground state, causing pyramidal inversion to be disfavored. The phosphine oxide 7 shows only a small increase in repulsion in going to the transition state, while the sulfonic acid 6 experiences large electrostatic repulsions in both the tetrahedral and the trigonal states. Since there is little difference in electrostatic repulsion in the latter two cases, the barrier to pyramidal inversion is low.

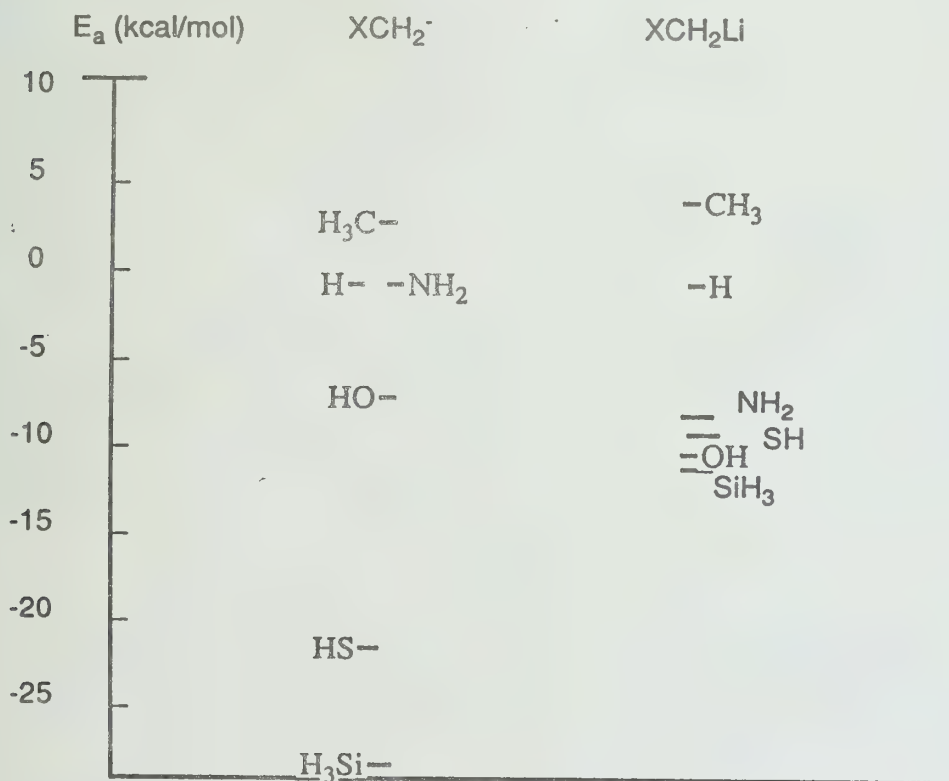
**Polarizability** - Some computational work has been done by Houk and Schleyer regarding the stability of  $\alpha$ -heteroatom carbanions as the free anion or as the lithiated species.<sup>10</sup> As shown in Scheme V, the best carbanion stabilizing group is silicon. This is due to the high polarizability of silicon and the low lying Si-H  $\sigma^*$  orbitals which allow stabilization by negative hyperconjugation. Sulfur displays similar properties in the free carbanion. Houk and Schleyer's calculations,<sup>10</sup> as well as those of several others,<sup>11</sup> show that heteroatom d orbitals do not contribute to stabilization of the carbanion.



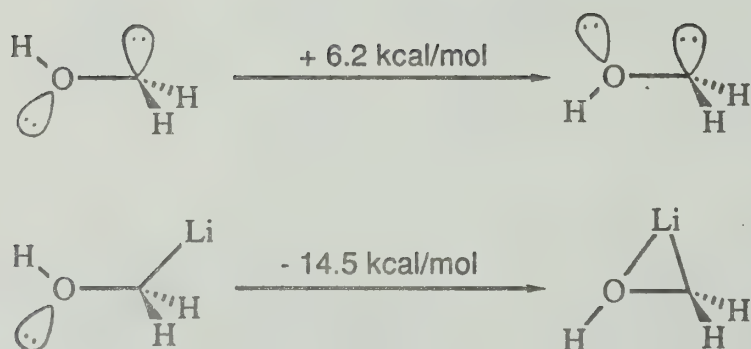
**Bridging** - Scheme V also shows that in some cases there are differences in the stabilities of the free anions as compared to the lithiated carbanions. This can be understood by considering the geometries of the carbanions. The increased stabilization of the  $\alpha$ -hydroxy and  $\alpha$ -amino lithiated carbanions is due to bridging (Scheme VI). The free carbanion prefers the anti geometry to minimize electrostatic repulsion. The lithiated carbanion prefers the bridged geometry by 14.5 kcal/mol over the anti geometry.

### SYNTHETIC APPLICATIONS

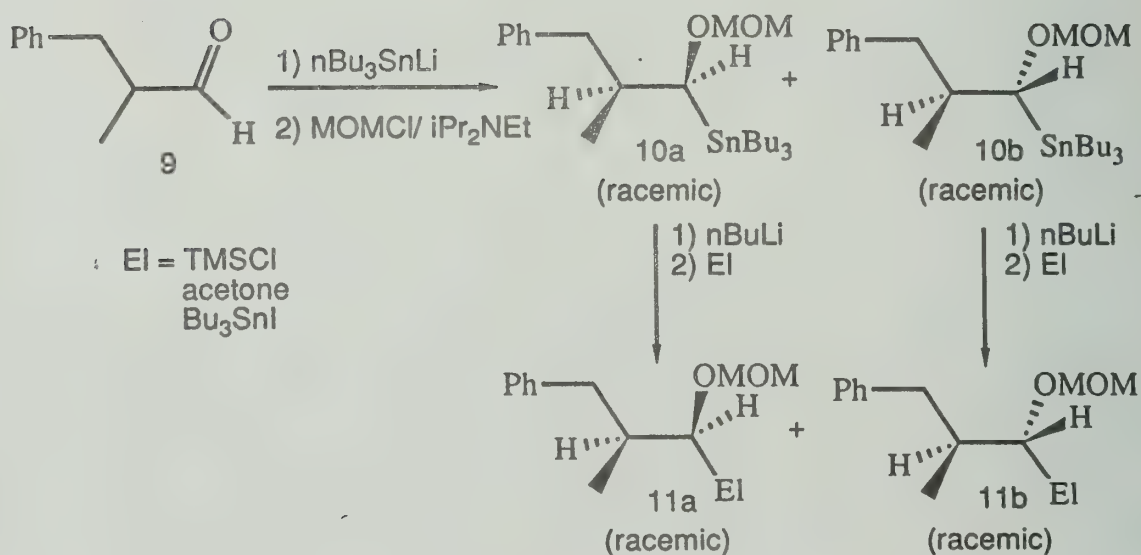
The use of  $\alpha$ -alkoxycarbanions has been mainly developed by Still<sup>12</sup> and McGarvey.<sup>13</sup> Treatment of 2-benzylpropanal **9** with tri-*n*-butylstannyl-lithium gives the corresponding alcohols which are protected as their MOM ethers **10**. The diastereomeric stannanes **10** are separated and transmetalated with *n*-butyllithium. The carbanions are treated with various electrophiles to give the products **11** with complete retention of configuration (Scheme VII).<sup>12a</sup>



SCHEME V.

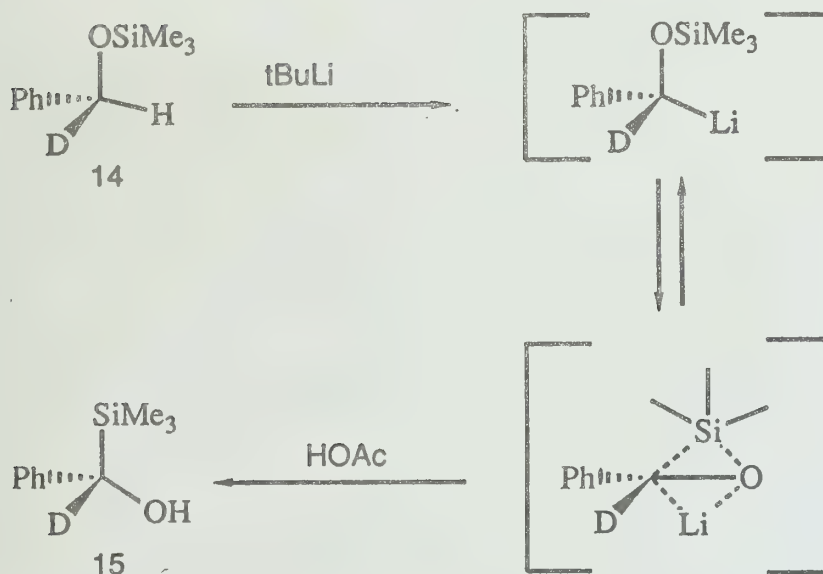
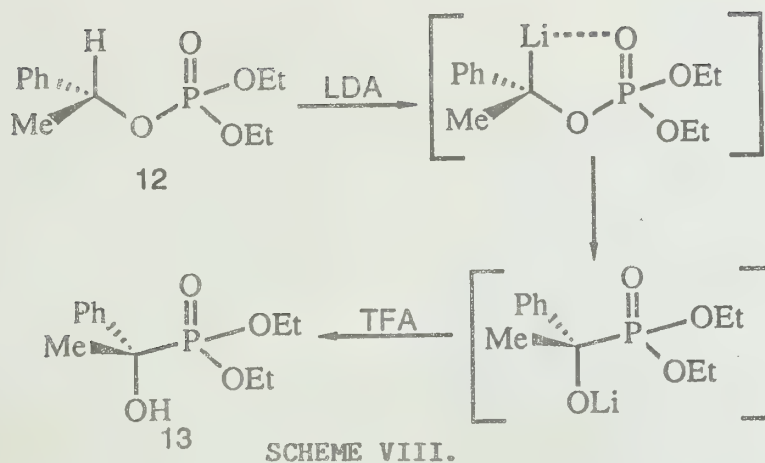


SCHEME VI.

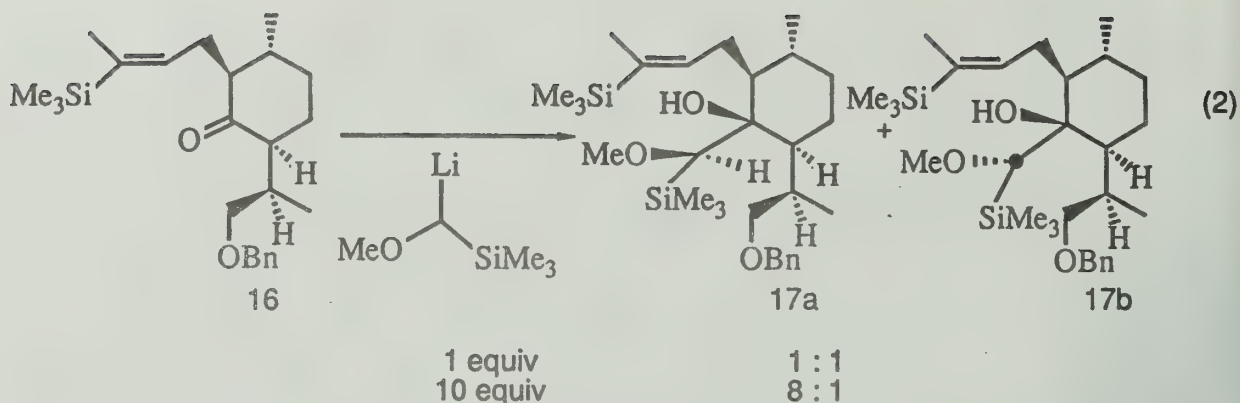


SCHEME VII.

Stereogenic carbanions have been used in reactions related to the Wittig rearrangement. Treatment of the optically active phosphate **12** with LDA generates the carbanion which rearranges to give the phosphonate **13**, without loss of stereochemistry (Scheme VIII).<sup>14</sup> An optically active trimethylsilylether **14** undergoes retro-Brook rearrangement upon treatment with *t*-butyllithium to give the optically active silane **15** without racemization (Scheme IX).<sup>15</sup>



Configurationally stable carbanions have been used in the total synthesis of qinghaosu (eq 2).<sup>16</sup> Reaction of one equivalent of racemic lithium methoxy(trimethylsilyl)methylide with the optically active ketone 16 gives a 1:1 diastereomeric mixture of axial alcohols 17. However the use of ten equivalents of the lithiated carbanion gives an 8:1 mixture of the corresponding alcohols 17 via kinetic resolution.



## CONCLUSION

The stability of alkyl carbanions is enhanced by the use of  $\alpha$ -heteroatoms. The electronegativity, polarizability, and bridging potential of the heteroatoms are the factors which account for the stability of the carbanion. These stereogenic carbanions have much synthetic potential which has just begun to be explored.

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## RECENT ADVANCES IN SYNTHESIS OF CORIOLIN

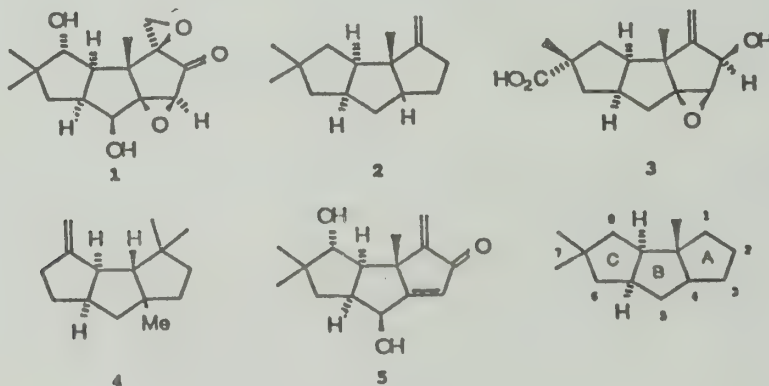
Reported by Andy Burke

April 27, 1987

## INTRODUCTION

The linear triquinane, Coriolin 1, is one member of the class of sesquiterpenes known as the hirsutanes. Other hirsutanes are hirsutene 2, hirsutic acid 3, and capnellene 4 (Scheme I). Coriolin was first isolated from fermentation broths of the Basidiomycete Coriolus consors by H. Umezawa in 1969<sup>1</sup> and was shown to have interesting antibacterial and antitumor properties.<sup>2</sup> The structure of coriolin was determined by spectroscopic analysis and chemical transformations in 1971,<sup>3</sup> and this structure was confirmed by X-ray crystallographic analysis in 1974.<sup>4</sup> The linear triquinanes, hirsutanes, contain the cis, anti cis-tricyclo-[6.3.0.0<sup>2,6</sup>]undecane ring system. With coriolin this ring system is highly functionalized and presents an intriguing target for synthesis. (The carbon numbering scheme and ring designations are shown in Scheme 1.)

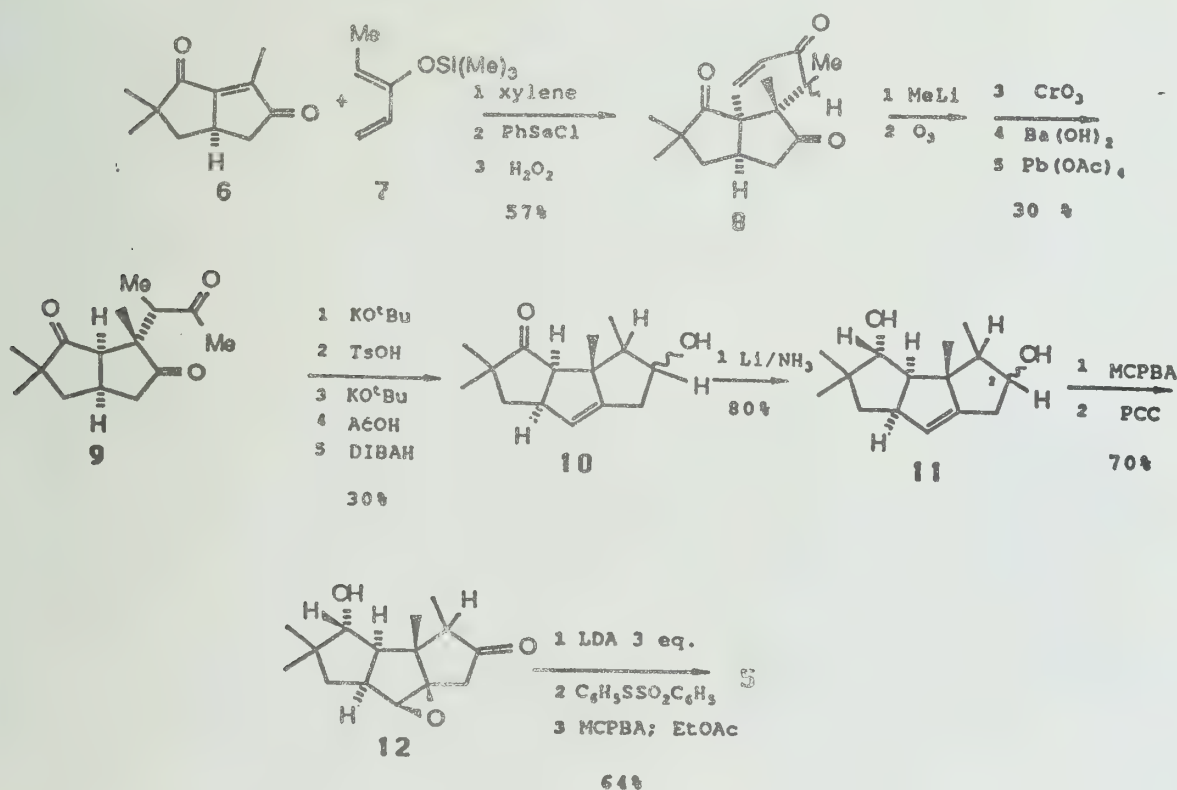
The highly oxygenated structure of 1 has eight stereocenters arrayed about the ring system. Two of the early attempts at synthesis were lengthy and were hampered by multiple protection and deprotection steps.<sup>5,6</sup> Although many successful syntheses of racemic coriolin have been described in the literature, only recently has an enantioselective approach to (-) coriolin been reported.<sup>7</sup> Many of the syntheses to racemic coriolin proceed via the cross-conjugated dieneone intermediate 5, termed "Danishefsky's intermediate".<sup>8</sup> The conversion of intermediate 5 into coriolin is accomplished by oxidation with alkaline H<sub>2</sub>O<sub>2</sub> in moderate yield. The two primary approaches in the construction of coriolin involve either alkylation or photochemical transformations.



SCHEME I

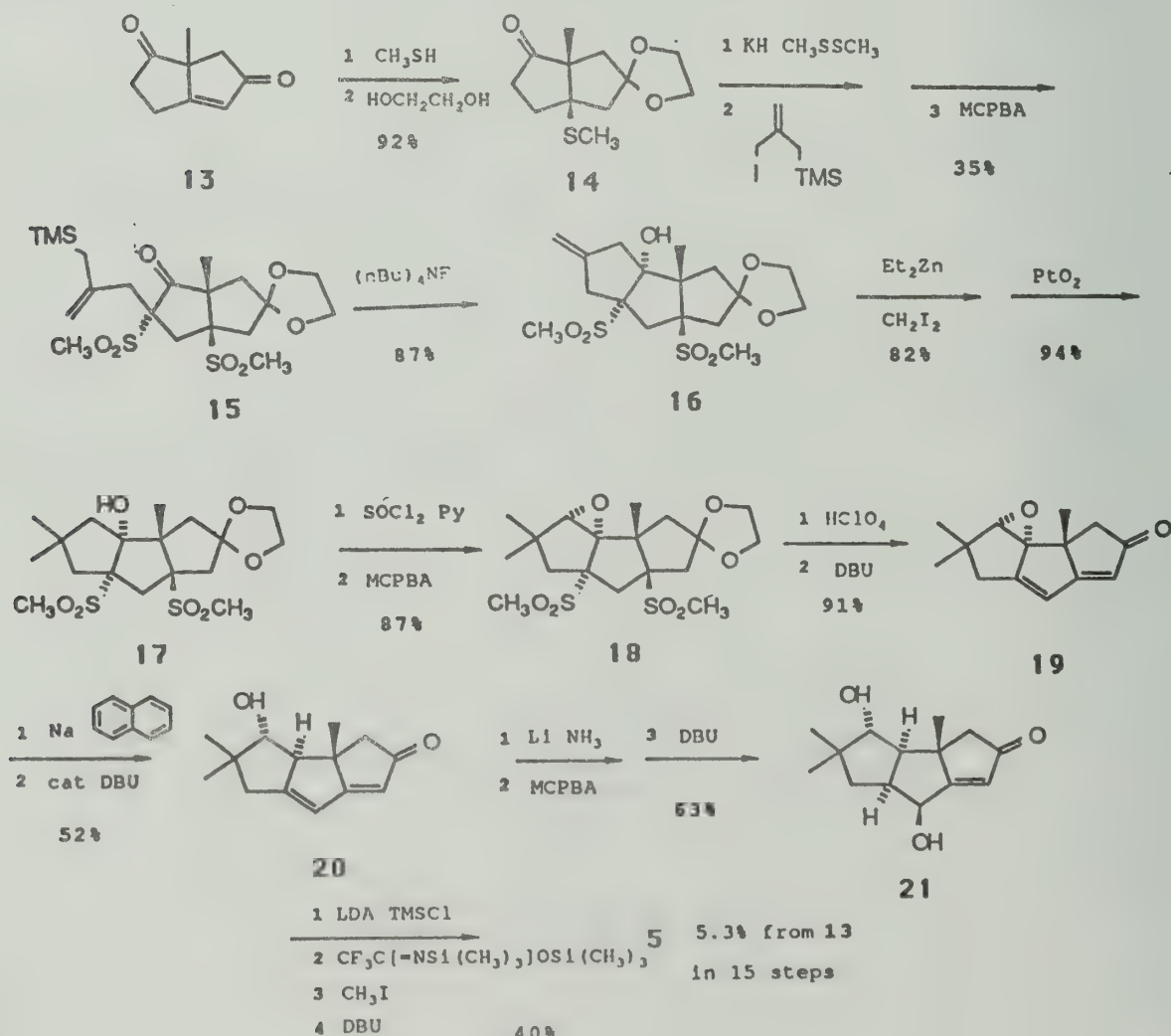
# ALKYLATION APPROACHES TO TRICYCLIC INTERMEDIATE 5

Danishesky approaches intermediate 5 using a cycloaddition (Scheme 2).<sup>8</sup> Cycloaddition of diene 7 and eneone 6 proceeded smoothly. Diene approach to 6 was predicted to occur on the  $\alpha$  face, as the alternate  $\beta$  approach would result in a trans fusion of the bicyclic BC ring system. After cycloaddition, treatment with phenylselenenyl chloride followed by oxidation gave 8 in 50% overall yield from 6. Selective addition of MeLi to the cyclohexeneone carbonyl, ozonolytic cleavage of the double bond, Jones oxidation, decarboxylation, and oxidation gave triketone 9 in 30% overall yield from 8. Deconjugation of the enone, followed by reduction gave the epimeric alcohols 10 in 85% yield. The stereochemistry at C 1 was undetermined. These epimers were separated, but the epimers converge later in the synthesis. Lithium in ammonia reduction of the crude epimers of 10 gave the more stable  $\alpha$  diol 11. Epoxidation and oxidation of the more accessible alcohol gave the desired  $\beta$  hydroxy ketone, 12. Since the alternative would require a trans fusion of rings A and B. Further functionalization of 12 generated the intermediate 5.



SCHEME II

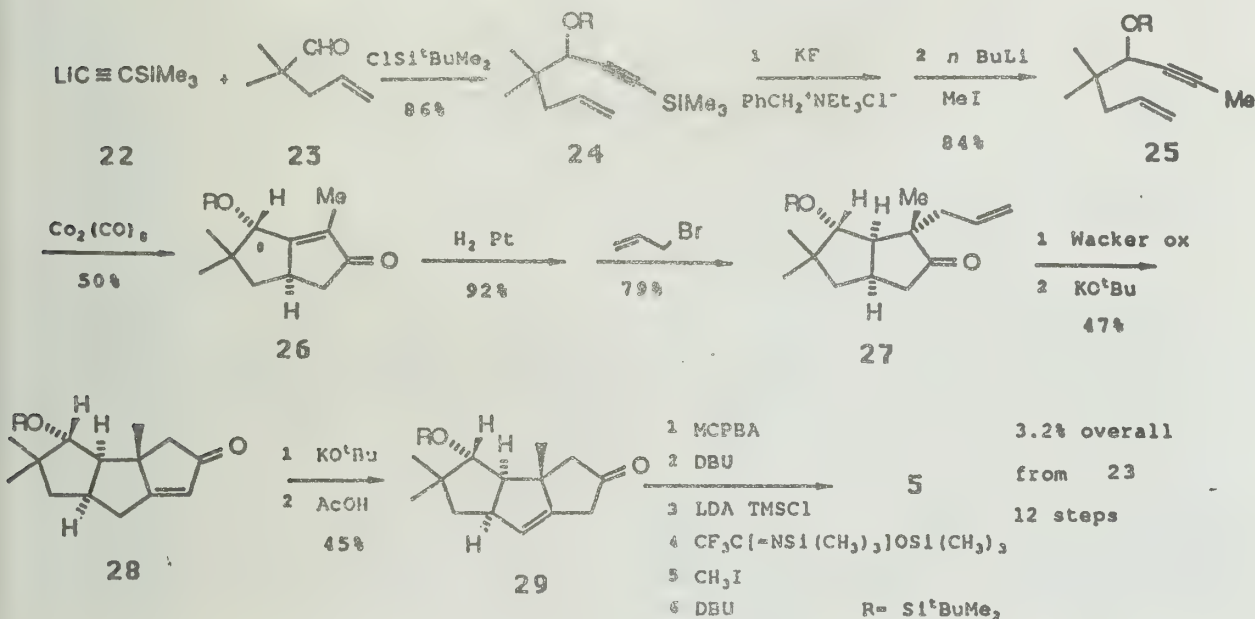
Trost approaches the synthesis of coriolin starting with enedione **13**, see Scheme III.<sup>9</sup> Addition of methanethiol, followed by selective ketalization gave monoketone **14**. Treatment of **14** with KH and alkylation, then oxidation with MCPBA gave the C ring precursor **15**. Cyclization was induced using fluoride to give **16**. The dimethyl substituent was introduced with a cyclopropanation followed by hydrogenolysis to give **17**. Dehydration and epoxidation gave the crystalline disulfone **18**, which after ketal hydrolysis underwent a double sulfone elimination to furnish dienone **19**. Hydrogenolysis of the allylic epoxide and isomerization of the double bonds gave **20**. The remaining hydroxyl group was introduced by a sequence involving a dissolving metal reduction, kinetic protonation to give the  $\beta,\gamma$  unsaturated eneone **20** which was then epoxidized and isomerized to furnish the allylic alcohol **21**. The last step was  $\alpha$ -methylenation of **21** to arrive at intermediate **5**. The overall yield of **5** from **13** was 5.3% in fifteen steps.



SCHEME III

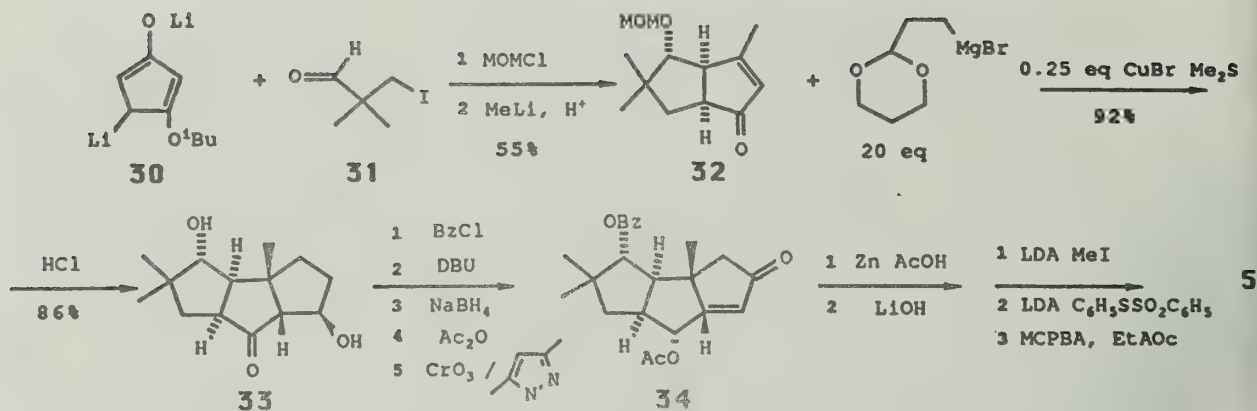


Magnus and coworkers generated the tricyclic precursor 5 using Pauson-Khand methodology (Scheme IV).<sup>10</sup> Addition of alkyne 22 to aldehyde 23 followed by protection gave enyne 24. Desilylation of the alkyne and alkylation gave enyne 25.  $\text{Co}_2(\text{CO})_8$  mediated cyclization gave the bicyclic enone 26 in a 4:1 ratio with the C-8 epimer. Hydrogenation and alkylation appending the last carbon unit gave ketone 27. Oxidation to the methyl ketone and ring closure gave the tricyclic ketone 28. Deconjugation, epoxidation, rearrangement and deprotection resulted in the desired intermediate 5. The overall yield of 5 from 22 was 3.2% in 12 steps.



**SCHEME IV**

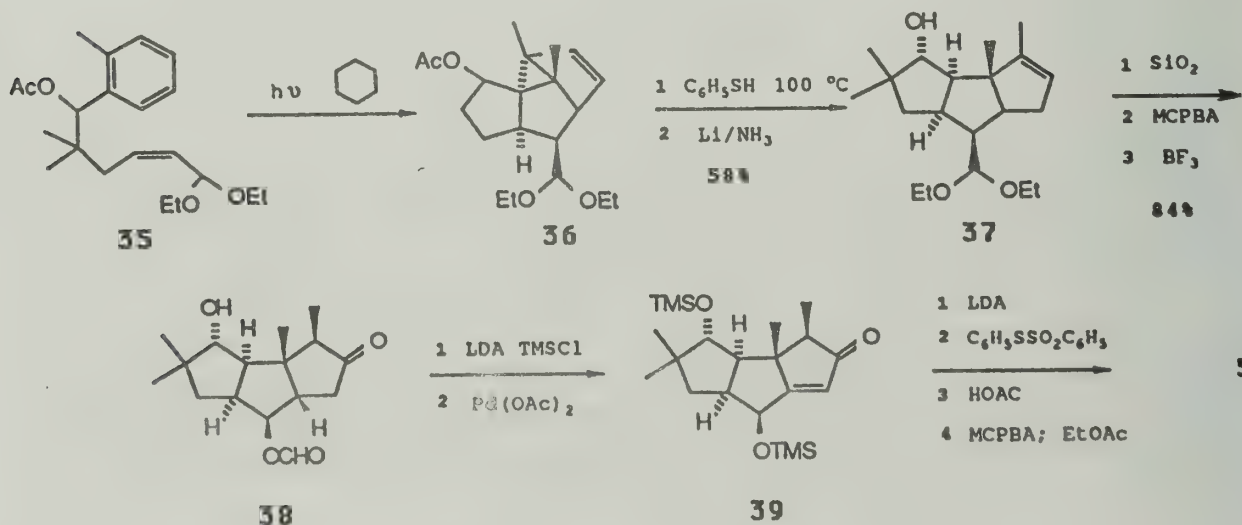
Koreeda and coworkers have utilized the dianion 30 in a two-stage, one pot addition-alkylation reaction on the  $\beta$ -iodoaldehyde 31 to generate a bicyclo[3.3.0]oct-3-ene-2-one (Scheme V).<sup>11,12</sup> Hydroxyl group protection, followed by methyllithium addition and acid treatment resulted in the formation of ketone 32. Cooper (I) catalyzed conjugate addition and acid catalyzed deacetalization and cyclization generated the tricyclic ketodiols, 33. After conversion to the protected enone, reduction, and acetylation, oxidation gave 34. Further manipulation and two stages of deprotection resulted in the formation of intermediate 5. The overall yield of 5 from 29 was 20.5% in 11 steps.



SCHEME V

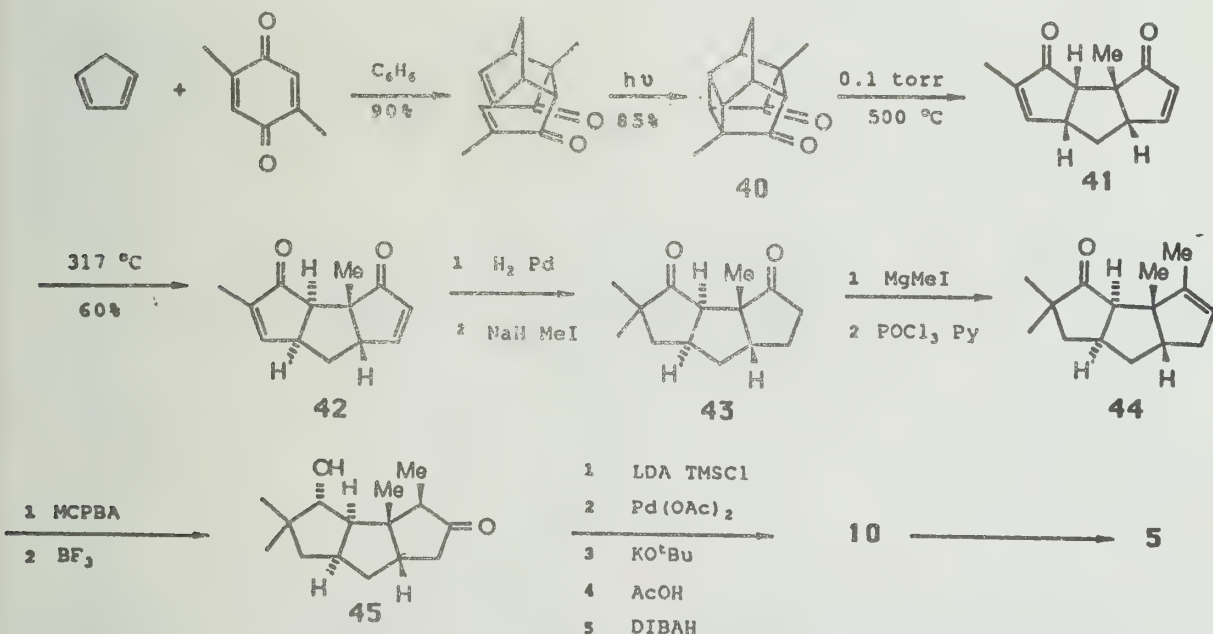
## PHOTOCHEMICAL APPROACHES TO TRICYCLIC INTERMEDIATE 5

Wender and coworkers have used an arene-olefin cyclization to generate the necessary carbon skeleton for coriolin (Scheme VI).<sup>13</sup> Using 35 as a starting material, they obtained the bridged tetracyclic structure 36 by photocyclization. Cleavage of the cyclopropane by thiyl radical addition, followed by Li/NH<sub>3</sub> reduction gave the fused tricycle 37. The acetal was hydrolyzed, and the resulting aldehyde was subjected to Baeyer-Villiger oxidation with concomitant epoxidation. After Lewis acid catalyzed rearrangement to the ketone 38, elaboration to the eneone 39 followed standard methods. Enone 39 was  $\alpha'$ -sulfenylated; oxidation, and elimination gave intermediate 5.



SCHEME VI

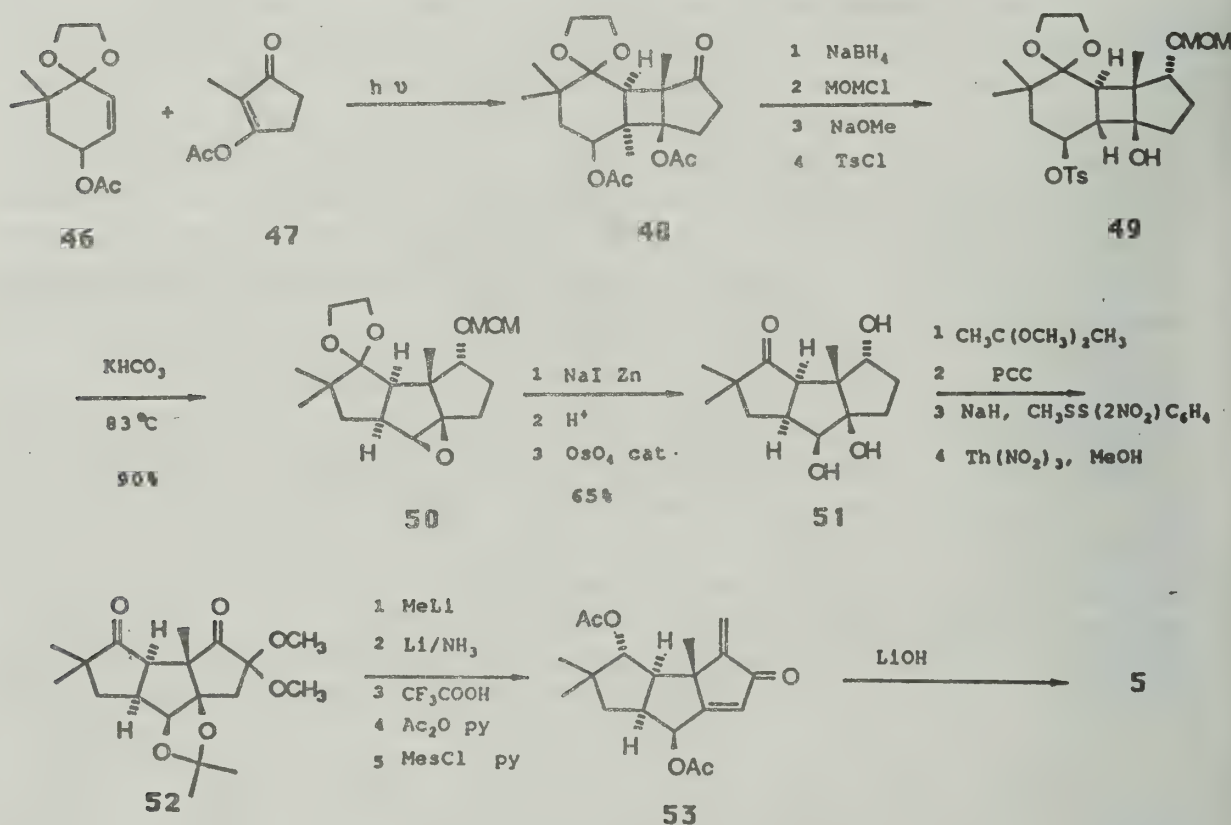
Mehta and coworkers used 1,3-cyclopentadiene and 2,5-dimethylbenzoquinone as starting materials. The only reagents needed to generate the desired carbon skeleton being heat and light (Scheme VII).<sup>14</sup> After a thermal [4+2] cycloaddition, then a photochemical [2+2] cycloaddition, the pentacyclic adduct **40** underwent a thermally-induced regioselective cyclobutane fragmentation to give the fused tricyclic bis enone **41**. However, this approach generates the *cis,syn,cis* triquinane skeleton, not the desired *cis,anti,cis* triquinane. Thermal isomerization of **41** did give **42**; other methods failed to effect the necessary isomerization. Bisdienone **42** was hydrogenated and alkylated to introduce the gem dimethyl group **43**. Addition of MeMgI to the less hindered ketone and dehydration gave olefinic ketone **44**. Dissolving metal reduction to give the more stable  $\alpha$  alcohol, followed by epoxidation and rearrangement gave ketone **45**. The remaining steps to **5** followed standard methods employing Danishefsky's intermediate **10**.



### SCHEME VII

Tatsuta and coworkers generated the tricyclic [6.3.0.0<sup>2,6</sup>] skeleton by the rearrangement of a tricyclic [6.3.0.0<sup>2,7</sup>] photoproduct (Scheme VIII).<sup>15</sup> Photocycloaddition of olefin **46** and enone **47** generated **48**. After reduction, protection, hydrolysis and tosylation, the 6,4,5 system **49** underwent rearrangement on treatment with base to epoxide **50**. The epoxide was deoxygenated to the olefin, followed by hydrolysis and *cis* hydroxylation then gave triol **51**. The *cis* stereochemistry at C 4 and C 5

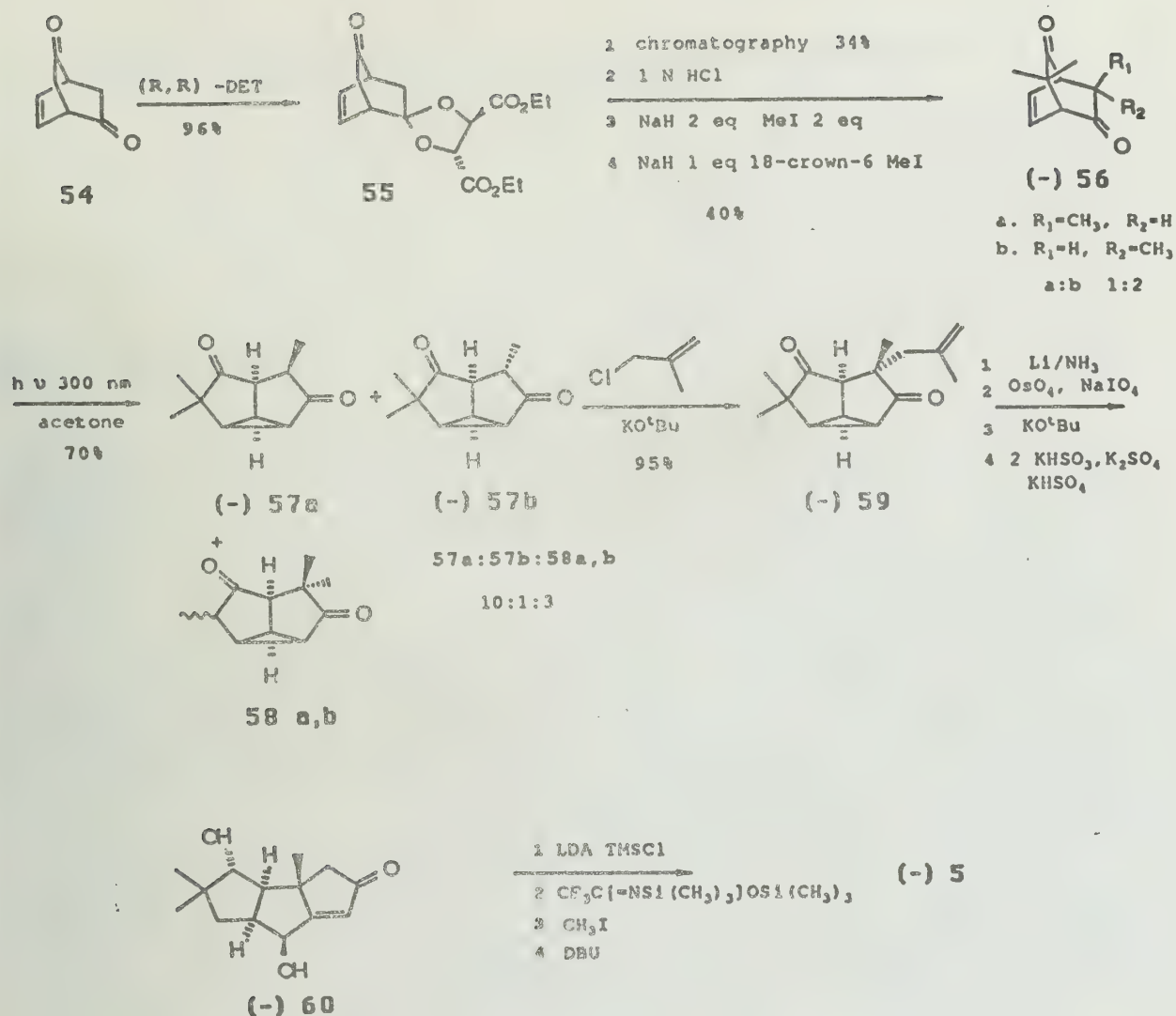
was achieved by the preferred formation of the cis fused bicycle through attack of  $\text{OsO}_4$  on the convex face. Triol 51 was protected as the acetone, oxidized, then converted to the ketal 52 in two steps. Addition of  $\text{MeLi}$  to the A ring ketone, reduction of C ring ketone, hydrolysis, acetylation and mesylation followed by elimination gave the dienone 53. Intermediate 5 was obtained by hydrolysis of the acetates.



### SCHEME VIII

Demuth and co-workers used a photochemical rearrangement to generate the carbon framework of the tricyclic dienone 5 (Scheme IX). This approach was used to prepare both racemic coriolin<sup>16</sup> and (-) coriolin.<sup>7</sup> The dione 54 was resolved by separation of the diastereomeric monoacetals 55. Thereafter hydrolysis and triple methylation gave a 1:2 ratio of diones 56a and 56b. The mixture was unfavorable for the planned oxadi- $\pi$ -methane photorearrangement. The rearrangement was preceded by a photochemical epimerization to give a 10:1:3 ratio of 57a, 57b, and 58a,b, respectively. Alkylation of the mixture of 57a,b gave diketone 59 as the single product. After dissolving metal reduction, oxidation, and cyclization, oxidation gave the enone 60. The enone 60 was converted following standard methods into intermediate 5.





Scheme IX

## SUMMARY

The synthesis of coriolin provides a test for cyclopentane formation methodology. Koreeda's synthesis is the most efficient approach to racemic coriolin. Demuth devised the first synthesis of coriolin in optically active form. Two of the photochemical approaches are hampered by the formation of isomers and the necessity of separation.

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GENERAL METHODS FOR THE ENANTIOSELECTIVE SYNTHESIS OF  
 $\alpha$ -AMINO ACIDS: GLYCINATE ALKYLATION AND  
ESTER AMINATION.

Reported by Peter E. Reed

April 30, 1987

I. INTRODUCTION.

Both natural and unnatural  $\alpha$ -amino acids are invaluable as pharmaceuticals, enzyme inhibitors, and probes of enzyme mechanisms. Since their biological activity is often restricted to one enantiomer, many methods of asymmetric synthesis have been developed for these compounds. Interestingly, however, few general methods are available for the asymmetric preparation of  $\alpha$ -unsubstituted amino acids, among them being asymmetric hydrogenation<sup>1</sup> and asymmetric transamination.<sup>2</sup> Recently, methods of asymmetric alkylation of glycine synthons and asymmetric  $\alpha$ -amination of acyl derivatives have been developed that allow the preparation of a wide variety of unsubstituted amino acids with a high level of enantiomeric purity. Furthermore, the general utility of both of these methods is enhanced by the existence of complementary methods that allow alternate nucleophilic/electrophilic partners to be used to prepare a given amino acid.

II. ALKYLATION OF NUCLEOPHILIC GLYCINATES.

**Bislactim Ethers of Cyclic Dipeptides.** Ulrich Schöllkopf and co-workers have prepared heterocyclic anions derived from cyclic dipeptides that react with electrophiles with a high degree of diastereoselectivity.<sup>3</sup> Subsequent hydrolysis provides amino acids with e.e.'s that are often in excess of 95%. A representative example is shown in Scheme 1. Thermal cyclization of the dipeptide L-Val-Gly-OEt gives the diketopiperazine 1, which is converted to the bislactim ether 2 by the action of Meerwein's salt. Deprotonation by n-butyl lithium occurs regiospecifically at the methylene carbon to give a diazapentadienyl anion, which is alkylated by electrophilic attack on the face opposite the isopropyl group. Hydrolysis of the resulting dihydropyrazine 3

liberates the newly-formed amino acid methyl ester **4** and allows recovery of the valine chiral auxiliary by distillation. The enantiomeric excess of the amino acid methyl esters obtained by this method is usually over 90% when benzyl, allyl, and propargyl halides are used as electrophiles, but is lower for alkyl halides (Table I). Purification of the diastereomeric intermediates in order to improve the optical purity of the final products has not been reported.

The bislactim ether **2**, derived from cyclo(L-Val-Gly), is most often used to prepare unsubstituted  $\alpha$ -amino acids. The bislactim ethers of cyclo(t-Leu-Gly)<sup>4</sup> and cyclo[(S)- $\alpha$ -methyl-(3,4-dimethoxy)-Phe-Gly]<sup>5</sup> have also been used, with the former system giving higher diastereoselectivities than **2**.

The high diastereoselectivity of the reaction of the anion of **2** with electrophiles is surprising considering the remoteness of the inducing stereocenter from the alkylation site. MO calculations place the largest coefficient and the highest electron density on N-1 in the HOMO of the anion (see numbering in Scheme 2). For this reason the metal counterion is assumed to be complexed to N-1 on the less hindered face, where it directs the incoming electrophile for attack by C-3 on this face.<sup>10</sup> The diastereofacial bias may be further enhanced by the orientation of the inducing substituent on the ring. NMR analysis of benzyl substituted 1,4-dihydropyrazines reveals that the aromatic ring is "folded" over the dihydropyrazine ring. Although no evidence for a folded orientation of the substituent in the anion of **2** has been obtained, a folded orientation would be expected to increase the diastereoselectivity of the reaction.

Scheme 1

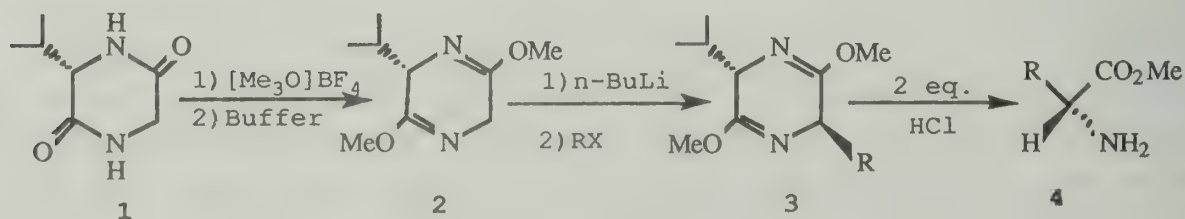




Table I: Some (R)-amino acid methyl esters (4) prepared from 2

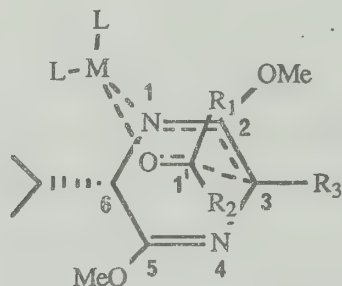
R	% e.e.	ref.	R	% e.e.	ref.
-CH <sub>2</sub> Ph	92-95	3	-CH <sub>2</sub> OCH <sub>2</sub> Ph	92	9
-CH <sub>2</sub> -(3,4-OMe)-C <sub>6</sub> H <sub>3</sub>	92	3	-CH <sub>2</sub> CH <sub>2</sub> PO(OEt) <sub>2</sub>	96	6
-CH <sub>2</sub> (2-naphthyl)	92	3	-CH <sub>2</sub> CH <sub>2</sub> OPO(OEt) <sub>2</sub>	92	6
-CH <sub>2</sub> C≡CPh	>95	3	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> N(Bn) <sub>2</sub>	58	6
-CH <sub>2</sub> C≡CH	65	3	-CH <sub>2</sub> (3-indoyl)	88	7
-CH <sub>2</sub> CH=CHPh	>95	3	-CF(Me) <sub>2</sub>	>95	8
-n-C <sub>7</sub> H <sub>15</sub>	80	3			

The anions derived from bislactim ethers react at C-3 with ketones and aldehydes to give addition products in good yields.<sup>11</sup> Ketones react with >95% d.e., and aldehydes with 80-90% d.e. at C-3. Dehydration of the addition products with SOCl<sub>2</sub>/2,6-lutidine prior to hydrolysis of the dihydropyrazine ring provides a route to  $\alpha$ -alkenyl glycine derivatives.<sup>12</sup> These  $\beta,\gamma$ -unsaturated amino acids can also be prepared from the reaction of a bislactim ether anion with 2-(*t*-butyldimethyl)silyl aldehydes or thioketones.<sup>11,13</sup>

Enantiofacial selectivity with respect to the carbonyl component of the aldol reaction varies widely with lithiated bislactim ethers (d.e. 4-87% at C-1'). The major epimer can be predicted from the transition state model depicted in Scheme 2.<sup>10</sup> The metal cation is positioned above N-1 of the dihydropyrazine ring and complexes with the oxygen of the carbonyl group, orienting the carbonyl carbon for reaction at C-3 in a chair cyclohexane-like transition state. When R<sub>3</sub> = H, aldehydes adopt an orientation where R<sub>1</sub> = H in order to minimize R<sub>1</sub>-L and R<sub>1</sub>-OMe 1,3 diaxial interactions; this results in the predominance of the (1'S) epimer. When R<sub>3</sub> = Me, aldehydes orient themselves so that R<sub>2</sub> = H in order to minimize the R<sub>2</sub>-R<sub>3</sub> torsional interaction, and the (1'R) epimer is the major product.

A dramatic increase in both the diastereoselectivity with respect to the anion and the enantioselectivity with respect to the carbonyl is seen when titanium is substituted for lithium in the aldol reaction. Titanium forms shorter oxygen-metal and nitrogen-metal bonds, resulting in a more compact transition state that gives higher levels of asymmetric induction. For example, in the addition of the anion of 2 to acetaldehyde, the titanium anion 2 gave a diastereomeric product ratio of (3*R*,1'*S*)/(3*R*, 1'*R*)/(3*S*,1'*S*)/(3*S*,1'*R*) = 91.6/1/0.3/0.3 compared to 57/14/0.6/1 for the lithium anion.<sup>14</sup> Subsequent hydrolysis yields diastereomerically pure D-threonine. The reaction of chiral aldehydes with the titanium anion of 2 can give diastereomerically pure products resulting from double asymmetric induction.<sup>15</sup>

Scheme 2

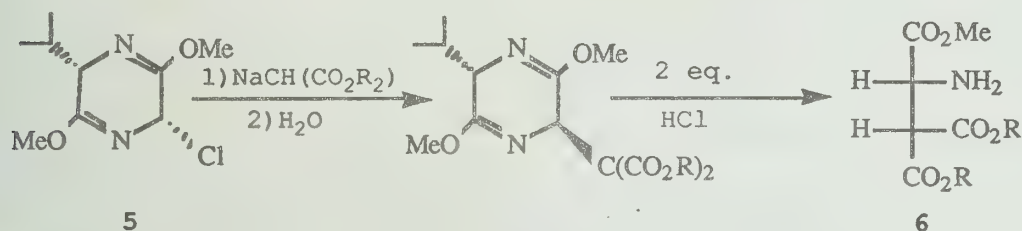


**Other Nucleophilic Glycinates.** Few additional examples of chiral nucleophilic glycine equivalents of general applicability exist.<sup>16</sup> The anions of chiral Schiff bases of glycine are alkylated with moderate stereoselectivity, with some of the best results obtained from the Schiff base prepared from glycine t-butyl ester and (1*S*,2*S*,5*S*)-2-hydroxypinan-3-one.<sup>17</sup> Very recently, Seebach reported that the anion of the chiral glycine derivative (*S*)-1-benzoyl-2-(t-butyl)-3-methyl-1,3-imidizolidin-4-one is attacked by electrophiles with a very high degree of diastereoselectivity (>95%).<sup>18</sup>

### III. ALKYLATION OF ELECTROPHILIC GLYCINATES.

**Chlorobislactim Ethers.** Schöllkopf has extended the utility of his method by the preparation of the chlorobislactim ether **5** from the lithiated bislactim ether of cyclo(Val-Gly) and hexachloroethane.<sup>19</sup> This compound was reacted with sodium dialkyl malonates to provide, after hydrolysis,  $\beta$ -carboxyaspartic esters in moderate yield and high optical purity (Scheme 3).

Scheme 3



**Dihydrooxazinones.** Williams has reacted the brominated dihydrooxazinone **7**, prepared from (1*R*,2*S*)-1,2-diphenyl-2-aminoethanol, with a variety of nucleophiles to provide amino acids with very high enantiomeric purity in moderate yields (Table II, Scheme 4).<sup>20</sup> Poor yields result when highly basic organometallic reagents are employed for the alkylation, due to competing reduction of **7**. Compound **7** has been used to prepare (*R*)- and (*S*)-[2-<sup>2</sup>H<sub>1</sub>] glycine.<sup>21</sup>

Scheme 4

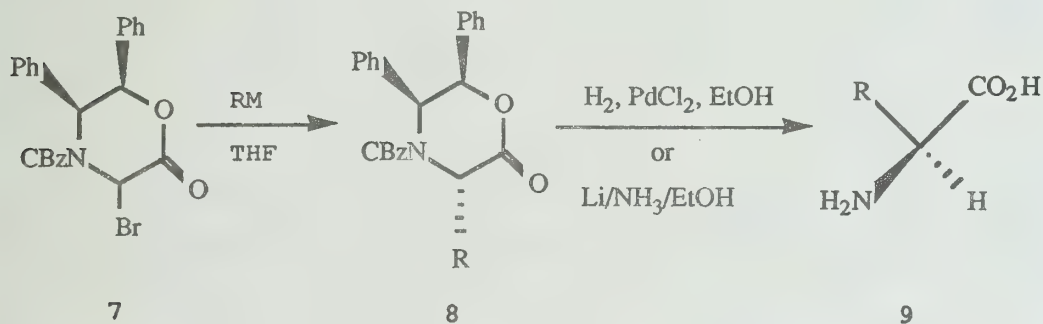
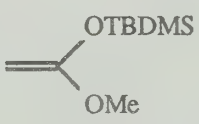
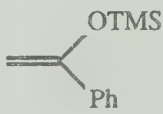



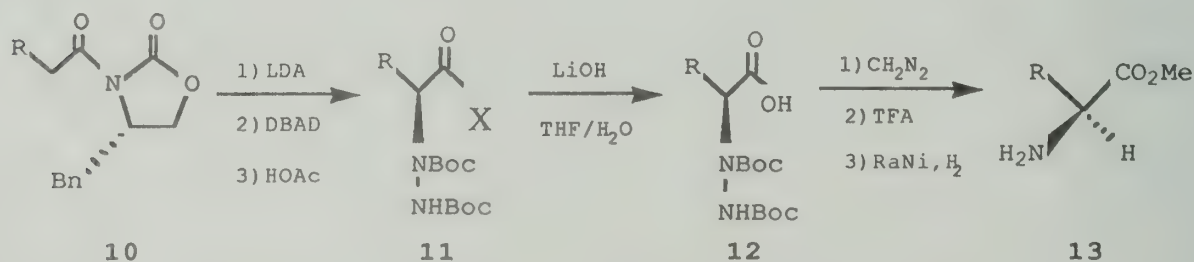
Table II: Amino Acids prepared from 7.

RM	% yield of 8	% e.e. of 9
	71	98.6 (R)
	54	96.9 (S)
	68	98.3 (S)
MeZnCl	46	96.8 (S)
Bu <sub>2</sub> CuCNLi <sub>2</sub>	48	99.5 (S)

## IV. AMINATION OF ENOLATES

**N-Acyloxazolidinone Enolates.** As an extension of his work on chiral enolates, Evans<sup>22</sup> has reported that the enolate of the phenylalanine-derived N-acyloxazolidinone **10** will react with the nitrogen electrophile di-tert-butyl azodicarboxylate (DBAD) to give the hydrazides **11** in very good chemical and stereochemical yield (Table III). Optical purity could be increased to >300:1 2*S*:2*R* diastereomeric ratio by silica gel chromatography. Most of the hydrazides undergo removal of the chiral auxiliary by means of hydrolysis, methanolysis, and transesterification to the benzyl ester with no detectable racemization. Furthermore, it was demonstrated that hydrazides of type **12** can be converted to amino acid methyl esters with negligible epimerization at C-2 (Scheme 5).

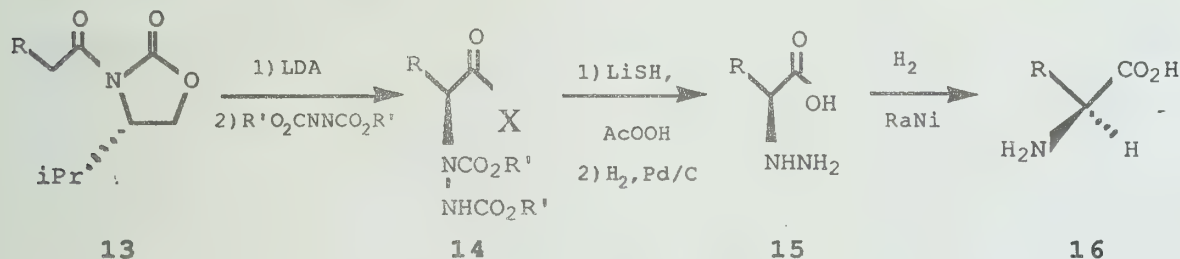
## Scheme 5





Vederas has studied the electrophilic amination of the enolates of valine-derived N-acyloxazolidinones (13).<sup>23</sup> Once again, high levels of asymmetric induction were observed in the hydrazide adducts (Table III). A variety of dialkyl azodiformates were used as electrophiles, with the largest d.e.'s resulting from the use of azodiformates possessing bulky alkyl groups. The hydrazide adduct diastereomers were reported to be difficult to separate by column chromatography. Cleavage of the oxazolidinones from the hydrazides 14 by transesterification to the benzyl ester proceeded with some racemization. However, less than 1% racemization was observed when lithium hydrosulfide was used to cleave the oxazolidinone. Compound 15 can be converted to its corresponding  $\alpha$ -amino acid by hydrogenation (Scheme 6).

Scheme 6



The diastereoselectivity of the reaction of N-acyloxazolidinone enolates is derived from the high *Z* stereoselectivity of enolate formation and the orientation of the enolate with respect to the oxazolidinone ring. Chelation of the lithium on the enolate oxygen to the carbamate carbonyl oxygen gives a conformationally rigid structure that is further stabilized by amide resonance.<sup>24</sup> Owing to the large diastereofacial bias conferred upon the enolate by this structure, electrophilic attack occurs on the least hindered face of the enolate with a high degree of stereoselectivity.

Table III: Amination of N-Acyloxazolidinone enolates.

oxazol- idinone	R	yield of hydrazide adduct 11 or 14	% d.e.	yield of acid 15	% e.e. of 15
10	-Me	92 %	96		
10	-CH <sub>2</sub> CHCH <sub>2</sub>	94	96		
10	-CH <sub>2</sub> Ph	91	94		
10	-Ph	96	94		
10	-CHMe <sub>2</sub>	95	96		
10	-CMe <sub>3</sub>	96	>98		
13	-Me	91	80	80 %	76
13	-CH <sub>2</sub> Ph	90	88	70	88
13	-CHMe <sub>2</sub>	85	94	84	94

**N-Methylephedrine Ester (E)-Silyl Ketene Acetals.** Gennari<sup>25</sup> has found that (E)-silyl ketene acetals derived from the (1*R*,2*S*)-N-methylephedrine esters 17 undergo asymmetric amination in the presence of TiCl<sub>4</sub>-DBAD complex to yield the hydrazido esters 18, which can be converted to amino acids of high enantiomeric purity (Scheme 7, Table IV). After removal of the chiral auxiliary, the enantiomeric excess can be improved to >98% by a single recrystallization of the intermediate hydrazino acids 19. Reduced yields of the hydrazide adducts are obtained when R is sterically demanding. Titanium tetrachloride is thought to serve as a stereochemical template for the reaction by ligating DBAD and the ephedrine dimethylamino group to form a cis octahedral complex from which the C-N bond is formed.

Scheme 7

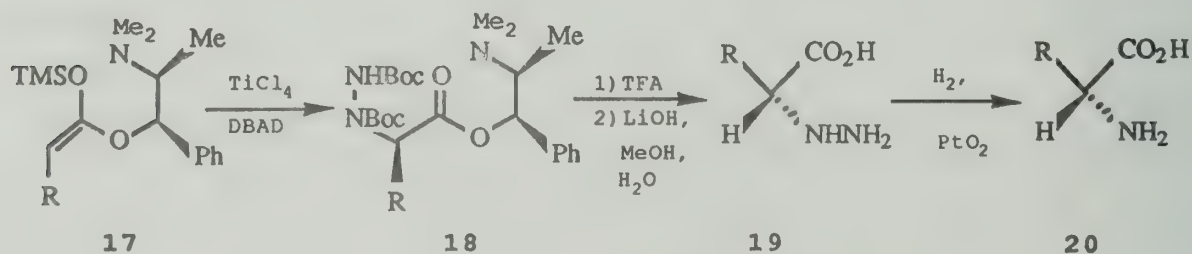


Table IV: Preparation of (R)-amino acids 20 from amination of 17

R	% yield 18	% yield 20	% e.e. of 20	
			from crude 19	from recryst. 19
-Me	70	72	90.6	>98
-CH <sub>2</sub> Ph	45	72	91.0	>98
-CH <sub>2</sub> CHMe <sub>2</sub>	70	74	81.5	>98
-CH <sub>2</sub> Me	65	74	84.0	>98
-CH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> Me	45	70	78.0	>98

V. AMINATION OF  $\alpha$ -HALOESTERS.

$\alpha$ -Halogenated 10-Sulfamidoisobornyl Esters. Oppolzer has employed ester derivatives of his chiral auxiliary 10-dicyclohexyl-sulfamoylisborneol 21 to prepare (R)- and (S)- $\alpha$ -amino acids (Table V).<sup>26</sup> This was accomplished by asymmetric halogenation followed by S<sub>N</sub>2 displacement by NaN<sub>3</sub> to form the C-N bond (Scheme 8). The crystalline nature of the isborneol esters was exploited to improve the overall amino acid e.e.'s by recrystallization of the intermediate products. The diastereoselectivity of the halogenation reaction is the result of the orientation of the (E)-silyl ketene acetal with respect to the chiral auxiliary, which is positioned so that complexation between the silicon and the sulfonyl oxygen is possible. In this orientation, the re-re face of the olefin is blocked so that the electrophile must approach from the si-si face. The chemistry of Oppolzer's chiral auxiliaries was described in a recent seminar by David Allen.<sup>28</sup>

Scheme 8

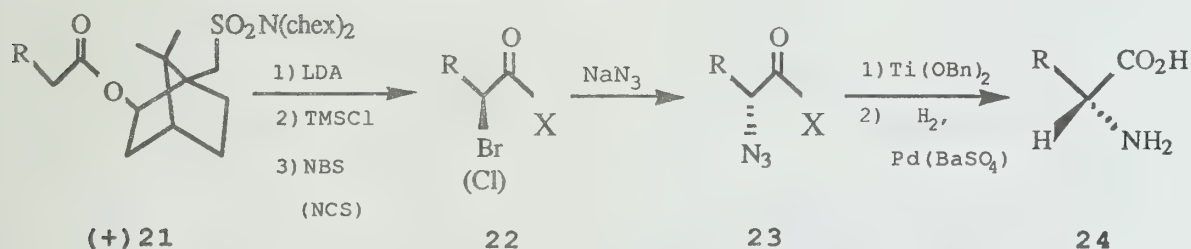


Table V: Preparation of (R)- and (S)-amino acids from 21

R	(+/-) 21	yield 22 cryst. (crude)	%d.e. 22 cryst. (crude)	yield 23 cryst. (crude)	%d.e. 23 cryst. (crude)	yield 24	%e.e. 24
n-Et	+	75 (87)	>99	87 (98)	-	72	94
n-Pr	+	75 (82)	96.7	93 (>99)	97 (96.7)	87	94
n-Bu	+	77	96	88 (93)	96	72	94
CH <sub>2</sub> CH(Me) <sub>2</sub>	+	72 (86)	>95	81 (97)	98 (96)	80	96
n-Hex	+	82	>93	89 (96)	100 (94)	78	98
CH <sub>2</sub> Ph	-	80 (92)	-	82 (>99)	98 (91)	72	95
CH <sub>2</sub> (1-ada- mantyl)	-	54 (64)	-	88 (>99)	-	73	96

## VI. CONCLUSION.

From the above examples it can be seen that either the amino group or the alkyl group can be incorporated asymmetrically into an amino acid to provide a wide range of common and uncommon amino acids. This new technology is a viable alternative to existing methods and can be expected to find application in synthetic, biological, and medicinal chemistry.

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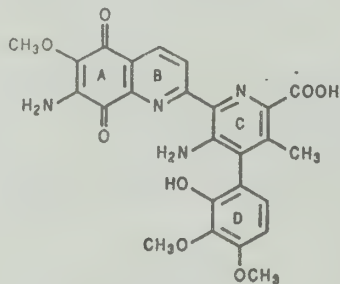
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## THE BIOSYNTHESIS OF THE ANTITUMOR ANTIBIOTIC STREPTONIGRIN

Reported by John Carney

May 4, 1987

Streptonigrin (**1**) is a metabolite of *Streptomyces flocculus*.<sup>1</sup> In addition to activity against a variety of Gram-positive and Gram-negative bacteria, **1** has pronounced activity against several human tumors<sup>2</sup> and is a potent inhibitor of reverse transcriptase.<sup>3</sup> The toxicity of **1**, however, has precluded its general clinical use. A number of syntheses of **1** have been reported,<sup>4</sup> and considerable effort has been made to prepare analogues with similar activity but reduced toxicity.<sup>5</sup> Several studies of structure-activity relationships have appeared,<sup>6</sup> and good progress has been made at understanding the toxicity of **1**.<sup>7</sup>

**1**

Biosynthetic studies of **1** have revealed that several previously unreported metabolic routes are operative. The four methyl groups of **1** derive from methionine,<sup>8,9</sup> and tryptophan is incorporated into rings C and D, but not into the quinoline portion.<sup>9</sup>

Substantial evidence implicates a  $\beta$ -carboline intermediate derived from a carboxylate AB-ring precursor and  $\beta$ -methyltryptophan as the source of the unusual pyridine C-ring.<sup>10</sup> These results suggest a new pathway for the formation of pyridine rings and a new metabolism of tryptophan.

Feeding studies using [U-<sup>13</sup>C<sub>6</sub>]-D-glucose<sup>11</sup> and [1-<sup>13</sup>C]-D-erythrose<sup>12</sup> further support the tryptophan origin of rings C and D and suggest that the biosynthesis of the quinoline portion occurs by shikimate-derived 4-aminoanthranilic acid (**2**) condensing with erythrose-4-phosphate, leading to 7-aminoquinoline-2-carboxylic acid (**3**). Both [4-<sup>15</sup>N] **2** and [4-<sup>2</sup>H] **3** have recently been shown to be incorporated into **1**, providing further evidence for the involvement of a new shikimic pathway product and a new biosynthetic route to quinolines.<sup>13</sup>

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## GERMANIUM: SOME USES IN ORGANIC SYNTHESIS

Reported by Lee A. Reif

May 7, 1987

## INTRODUCTION

Germanium is a IVB group element located between silicon and tin on the periodic table. Though its use in organic synthesis up until now has been sporadic, it often shows properties which are intermediate between those of the frequently-used silicon and tin reagents and thus it may, under certain conditions, have advantages.

Elemental germanium, predicted to exist by Mendeleev in 1871 and discovered by C. Winkler in 1886, is a gray-white, brittle, crystalline metalloid. It is obtained commercially from flue dust of smelters processing zinc ores and can be recovered from the by-products of coal combustion; its presence in coal insures a large reserve of the element. The major use for germanium is in the semiconductor industry, and its low toxicity in mammals, coupled with its marked activity against certain bacteria, suggests potential uses in chemotherapeutic agents.<sup>1</sup>

Table I: Properties of IVB group elements

Element	Bond energy to carbon (kcal/mol) <sup>2</sup>	Covalent radius (Å) <sup>2</sup>	Electronegativity <sup>3</sup>
C	85	0.77	2.5-2.6
Si	60-80	1.17	1.8-2.0
Ge	61	1.22	1.7-2.3
Sn	46	1.40	1.7-2.0
Pb	31	1.44	1.8-2.4

Some properties of the IVB group elements are shown in Table I. As can be seen, there is a steady decrease in C-element bond energies and an increase in the covalent radii. The trend of the electronegativity of these elements is not totally agreed upon. Although carbon is generally accepted to be the most electronegative of the set, evidence suggests that germanium may be more electronegative than silicon or tin.<sup>4</sup>

Germanium reagents are becoming increasingly important in the field of organometallic chemistry. Typical starting reagents such as triaryl- and trialkylgermanium halides and hydrides are available at prices ranging from \$6 to \$30 a gram.<sup>5</sup> These reagents can be converted into useful organometallic compounds which can be used for further transformation.

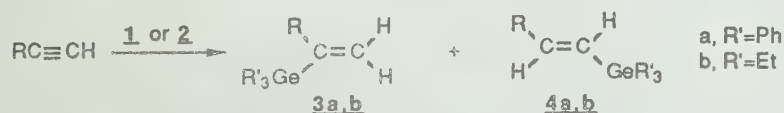


## VINYLGERMANES

**Preparation of vinylgermanes** - Oshima and coworkers have done extensive work on the preparation of vinylgermanes and have studied their reactivity relative to vinylsilanes. One preparative method employs the germylcopper reagents **1** and **2** shown below.

**1****2**

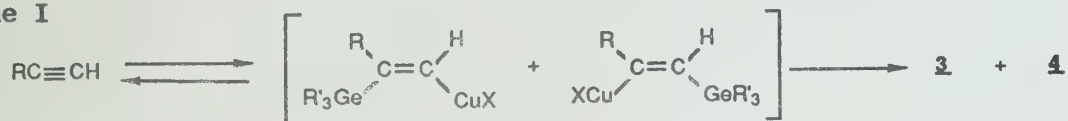
Reagent **1**, prepared from  $\text{Ph}_3\text{GeLi}$  and  $\text{CuCN}$ , reacts with terminal acetylenes in the presence of a proton donor, to yield a mixture of 2-triphenylgermyl-1-acetylenes **3a** and 1-triphenylgermyl-1-acetylenes **4a** in the ratios and yields shown in Table II.

Table II: Germylcupration of terminal acetylenes<sup>6</sup>

R	R' <sub>3</sub> GeLi	Cu Salt	Additive	Yield (%)	Ratio 3/4
n-C <sub>10</sub> H <sub>21</sub>	Ph <sub>3</sub> GeLi	CuCN	n-BuOH	71	80/20
	Ph <sub>3</sub> GeLi	CuCN	n-BuCHO	99	70/30
	Et <sub>3</sub> GeLi	CuBrSMe <sub>2</sub>	—	81	70/30
Ph	Ph <sub>3</sub> GeLi	CuCN	n-BuOH	85	<5/95
	Et <sub>3</sub> GeLi	CuBrSMe <sub>2</sub>	—	91	15/85

The presence of a proton donor, such as an alcohol or carbonyl compound, proved to be essential for formation the **3a** and **4a** from **1**; without these donors, only starting material was recovered. These results indicate that the reaction of **1** with terminal alkynes is reversible, with the equilibrium favoring starting material over the vinylcopper intermediate (Scheme I).<sup>6</sup>

Scheme I



As can be seen in Table II, reagent **2** was also effective in the formation of vinylgermanes. Unlike reagent **1**, however, no proton donor was required, so the intermediate copper species can be trapped with various electrophiles (Table III).<sup>6</sup> Similar methods are used to prepare vinylsilanes<sup>7</sup> and vinylstannanes<sup>8</sup> with generally comparable results.

Table III: Results from electrophilic trapping of alkenyl copper species<sup>6</sup>

$$\text{RC}\equiv\text{CH} \xrightarrow[2) \text{E}^+]{1) \text{2}} \begin{array}{c} \text{Ph} \\ | \\ \text{Et}_3\text{Ge}-\text{C}=\text{C}-\text{H} \\ | \quad | \\ \text{E} \quad \text{E} \end{array} \quad \text{5} \quad + \quad \begin{array}{c} \text{Ph} \\ | \\ \text{E}-\text{C}=\text{C}-\text{H} \\ | \quad | \\ \text{E} \quad \text{GeEt}_3 \end{array} \quad \text{6}$$

E	5/6	Yield (%)
D <sub>2</sub> O	7/93	89
Mel	17/83	82
H <sub>2</sub> C=CHCH <sub>2</sub> Br	10/90	96

Other methods for the preparation of vinylgermanes developed by Oshima and coworkers involve the platinum-catalyzed hydrogermylation of acetylenes (Scheme II), which depending on catalyst chosen, can give yields greater than 90% (H<sub>2</sub>PtCl<sub>2</sub>·6H<sub>2</sub>O), with an isomer ratio for **7/8** of 20/80. Compound **9** was not observed under these conditions. Changing catalysts to PtCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> lowers yields to near 50%, but gives only terminal germanes, **8** and **9**, in a ratio of 10/90 respectively.<sup>9</sup>

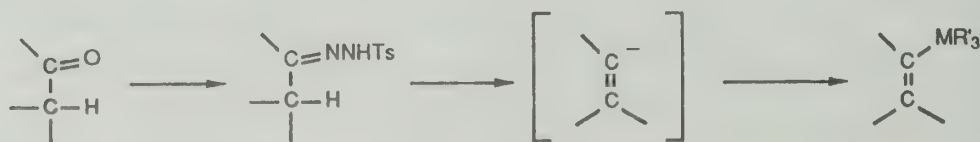
## Scheme II



Hydroalumination and hydroboration of germylacetylenes, prepared from the alkyne Grignard reagent and the trialkylgermanium halide, provide isomerically pure Z-olefins in yields up to 96%, and allow electrophilic trapping of intermediates leading to more highly substituted olefins.<sup>9</sup> Once again, analogous methods are used in the preparation of vinylsilanes.<sup>10,11</sup>

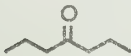


A different approach to vinylgermanes, utilizing ketones as starting material, was developed by Paquette and coworkers. In their procedure, keto-tosylhydrazones were treated with BuLi in TMEDA to form the vinyl anion; this anion was then allowed to react with Me<sub>3</sub>MX (M=Si, Ge, Sn) reagents, yielding the vinyl compound with the metal bonded to the original carbonyl carbon (Scheme III). The reaction is regioselective,

## Scheme III



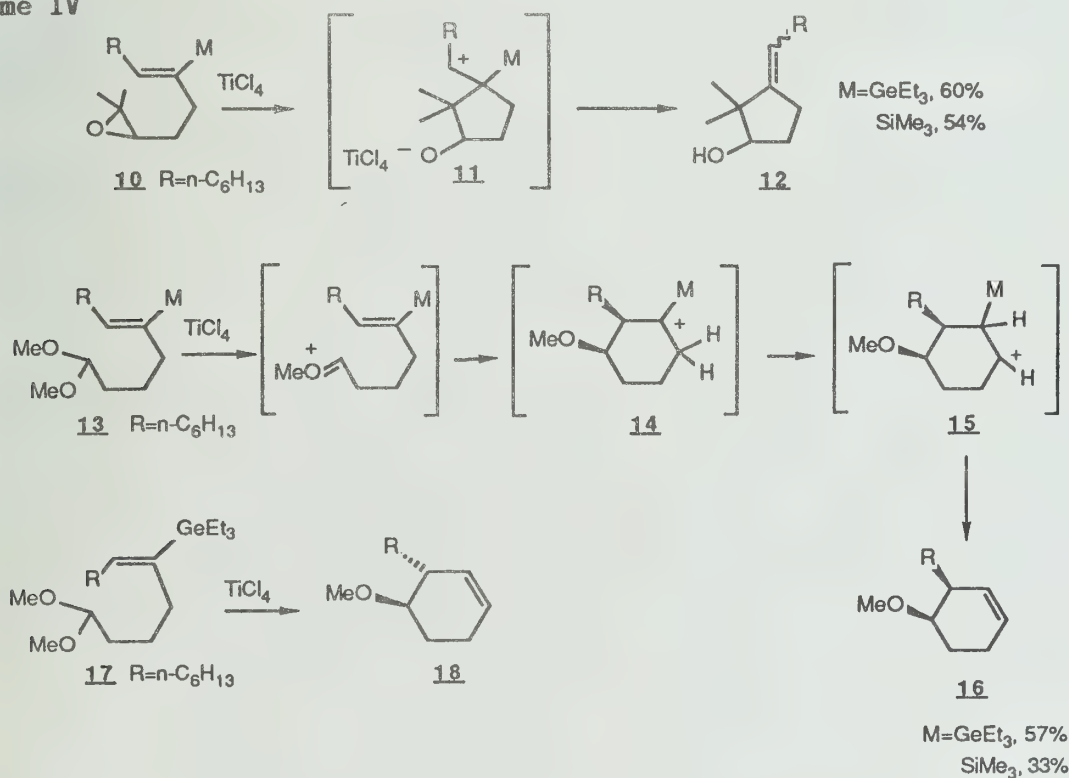
with proton abstraction from the less substituted carbon providing a single product.<sup>12</sup> As can be seen in Table IV, the germanium reagent yields are generally slightly higher than either the silanes or the stannanes.

Table IV: Ketone enmetalations<sup>12</sup>

Ketone	Vinylgermane Yield (%)	Vinylsilane Yield (%)	Vinylstannane Yield (%)
	47	38	43
	64	62	56
	58	71	-

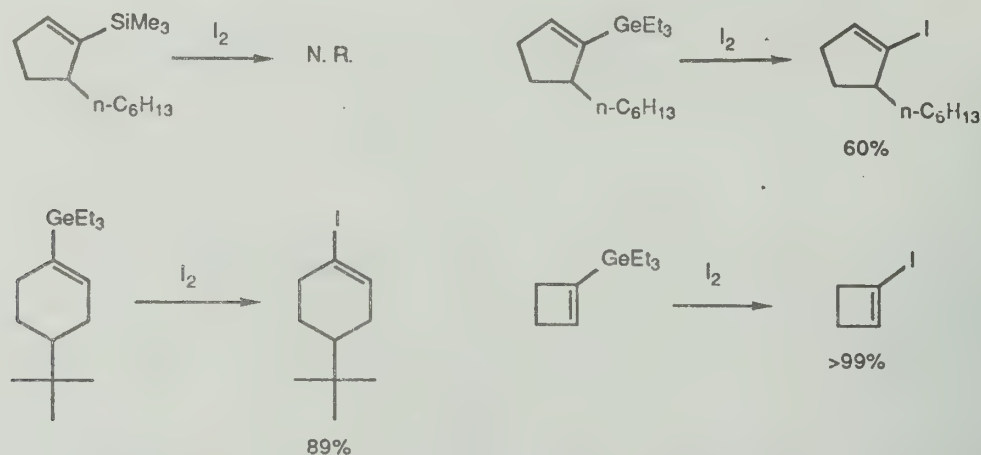
**Reactions of vinylgermanes** - The relative reactivity for the intramolecular reaction of vinylgermanes and vinylsilanes toward carbon electrophiles have been studied by Oshima, et al.<sup>13</sup> They found that treatment of epoxide **10** with  $\text{TiCl}_4$  gave exclusively the five-membered ring product **12**, concluding that the reaction must proceed through the relatively stable  $\beta$ -metal cation, **11** (Scheme IV). The use of  $\text{GeEt}_3$  provided somewhat higher yields than  $\text{SiMe}_3$ .<sup>13</sup>

Scheme IV



In contrast, compound **13** yields product **16** (Scheme IV). The authors suggest that this reaction proceeds by a cyclization to an  $\alpha$ -metal cation **14**, which may be kinetically preferred over the  $\beta$ -cation in this system.

**Scheme V**



Rearrangement to the more stable  $\beta$ -cation, **15**, by a hydride shift is followed by degermylation to **16**. As the conversion of **17** to **18** shows, the reaction proceeds with high stereospecificity. Attempts to change the ring size by increasing or decreasing the number of methylene groups gave complex product mixture with no cyclized products.<sup>13</sup>

The halodegermylation of vinylgermanes shows advantages over their analogous vinylsilanes. For instance, though acyclic vinylsilanes are easily converted to vinylhalides, cyclic vinylsilanes, shown in Scheme V, typically do not react with  $I_2$ .<sup>13</sup> Cyclic vinylgermanes, on the other hand, are converted by  $I_2$  into their corresponding iodides in good yield.<sup>13</sup>

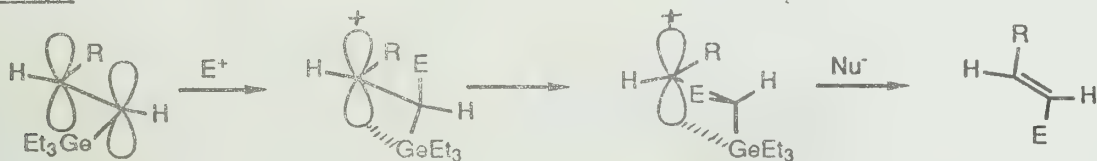
Iododegermylation of both di- and trisubstituted acyclic vinylgermanes generally proceeds in high yield (80-100%) with retention (>95%), while bromodegermylation typically proceeds with inversion, and the nature of the substrates can affect the stereochemical outcome.<sup>9</sup> Retention of stereochemistry seems best explained by the Koenig and Weber proposal for deuterodesilylation of analogous vinylsilanes with  $DCl$ . Retention in this system may be accounted for by simultaneous electrophilic addition to the double bond with rotation of the developing carbon-carbon single bond in the direction that will allow the trialkylgermanium group to stabilize the developing  $\beta$ -carbonium ion by bridging or hyperconjugation of the Ge-C bond. Attack by the nucleophile at germanium leads to product (Scheme VI).<sup>14</sup> This would be more likely to occur if the counter ion of the electrophile is sufficiently large to make addition to the carbonium ion kinetically less competitive with elimination of the trialkylgermane.<sup>15</sup>



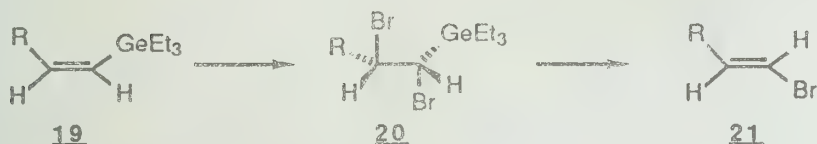
Inversion of stereochemistry is attributed to anti-addition of  $\text{Br}_2$  followed by anti-elimination. In fact, when compound **19** was treated with bromine, the anti-adduct intermediate **20** could be isolated and then converted with silica gel to **21** (Scheme VI).<sup>9</sup>

#### Scheme VI

##### RETENTION



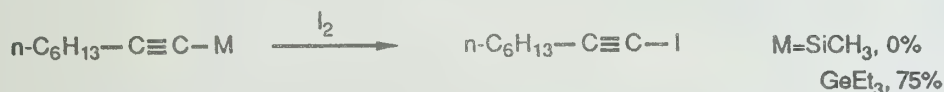
##### INVERSION



The substitution of the germyl group in olefins by halogen proceeds more easily and with better stereocontrol than does the corresponding silyl group. For instance, iodination of trisubstituted vinylsilanes gives only 60-81% yields with high stereoselectivity and retention.<sup>15</sup> Iodination of disubstituted vinylsilanes shows retention with yields of about 60% using  $\text{I}_2$  and  $\text{CH}_2\text{Cl}_2$ ; and inversion with yields of 80% using  $\text{I}_2$ ,  $\text{CF}_3\text{CO}_2\text{Ag}$ , and  $\text{CH}_2\text{Cl}_2$ , followed by  $\text{KF} \cdot 2\text{H}_2\text{O}$ ,  $\text{DMSO}$ .<sup>9a</sup> Bromination of Z-trisubstituted vinylsilanes was found to be very difficult while the E-olefins gave yields of 65-87% with inversion.<sup>15</sup> Finally, bromination of the disubstituted vinylsilanes showed yields of about 80% with inversion.<sup>11a</sup>

In a related study, Oshima et al. also found that  $\text{C}(\text{sp})\text{-Ge}$  bonds are cleaved by  $\text{I}_2$  much more easily than  $\text{C}(\text{sp})\text{-Si}$  bonds (Scheme VII).<sup>13</sup>

#### Scheme VII

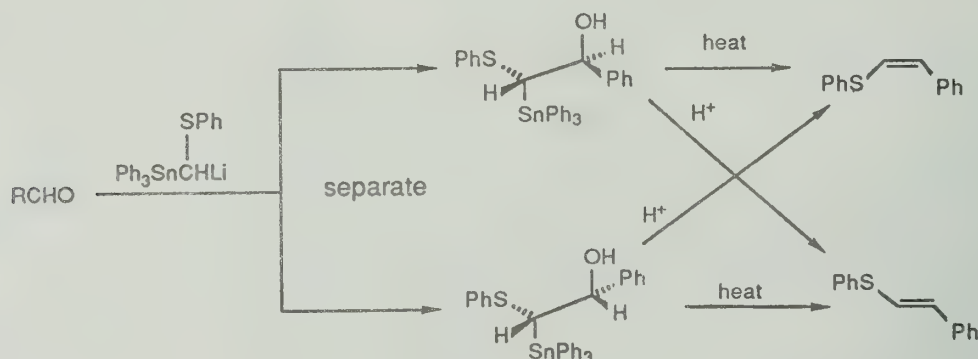


#### CARBONYL OLEFINATIONS

Another area in which germanium has shown considerable promise is in carbonyl olefinations. Work in this area with phosphorous reagents (Wittig) and silicon reagents (Peterson) is well known. Over the last decade, Kauffmann and coworkers have expanded the use of heavy-main group reagents, including Ge, Sn, Pb, As, Sb, Bi, Se, and Te in organic synthesis.<sup>16</sup>

One of the first heavy-main group elements used for carbonyl olefinations was the tin derivative  $\text{Ph}_3\text{SnC}(\text{SPh})\text{HLi}$ , which gives mixtures of the diastereomeric alcohols shown in Scheme VIII. After being separated, these alcohols could be converted to either Z or E olefins by syn- or anti-eliminations, depending on reaction conditions chosen.<sup>17</sup>

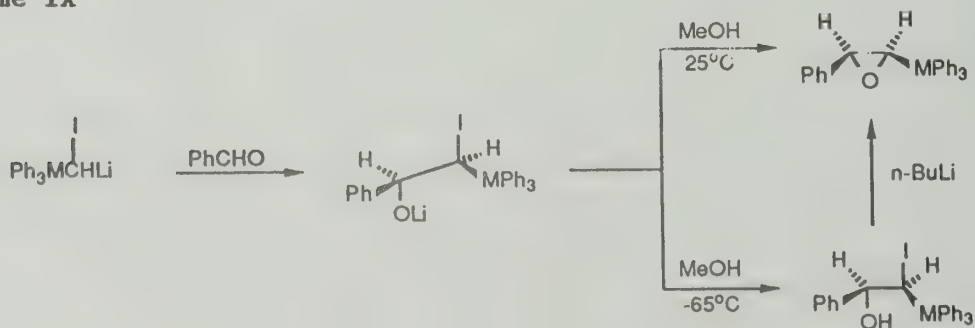
Scheme VIII



It was then discovered that several reagents of the type  $\text{Ph}_3\text{MC}(\text{I})\text{HLi}$  were more effective in producing olefin derivatives (epoxides and iodohydrins) stereospecifically. The silicon and germanium derivatives of these reagents form the Z-oxiranes exclusively when the intermediate aldehyde adduct is quenched with MeOH at room temperature; quenched with MeOH at  $-65^\circ\text{C}$ , only the threo-iodohydrin is isolated. This iodohydrin can be converted into the Z-oxirane with one equivalent of BuLi at room temperature (Scheme IX).<sup>18</sup>

The use of the Z-oxirane described above makes it possible to obtain either the E or Z olefins without separating a diastereomeric mixture of olefin precursors. In the case of the silyloxirane, ring opening with PhLi is followed exclusively by syn-elimination. This is complemented nicely by the germyloxirane in which ring opening with PhSNa is followed by anti-elimination upon treatment with perchloric acid. The behavior of the tin analog is under study.<sup>17</sup>

Scheme IX



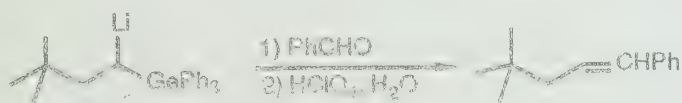
The germanium and silicon reagents discussed above are not suitable for aldehyde selective olefinations in the presence of a ketone, since both functional groups react rapidly. However, Kauffmann and coworkers were able to carry out selective aldehyde olefinations using the following reagents:  $\text{Me}_3\text{GeCH}_2\text{TiCl}_3$ ;  $\text{Me}_3\text{GeCH}_2\text{CrCl}_2$ ;  $\text{Me}_3\text{SiCH}_2\text{TiCl}_3$ ;  $\text{Me}_3\text{SiCH}_2\text{CrCl}_2$ . These reagents are generated in situ from  $\text{Me}_3\text{MMgBr}$  by reaction with  $\text{TiCl}_4$  or  $\text{CrCl}_3$ . Some representative yields are shown in Table V.<sup>19</sup>

Table V: Aldehyde selective olefinations<sup>19</sup>

Carbonyl	Yield (%) with $\text{Me}_3\text{SiCH}_2\text{TiCl}_3$	Yield (%) with $\text{CH}_3\text{GeCH}_2\text{TiCl}_3$
Heptanal	65	88
Octanal	59	75
Nonanal	41	76
Benzaldehyde	59	76
3,3-dimethyl-2-butanone	0	0
4-(t-butyl)cyclohexanone	0	0

Kauffmann and coworkers have also investigated the preparation of non-terminal olefins. The substituted tin and lead reagents did not work well for this purpose, but  $\alpha$ -lithiated germanium alkanes such as  $\text{RCH}_2\text{CHLiGePh}_3$  or  $\text{CH}_3\text{CHLiGePh}_3$  show promise. It remains to be determined whether these reagents offer advantages over the cheaper silicon analog. The only olefination that has been carried out (Scheme X) shows high yield and selectivity.<sup>16a</sup>

#### Scheme X



#### ARYL GERMANES

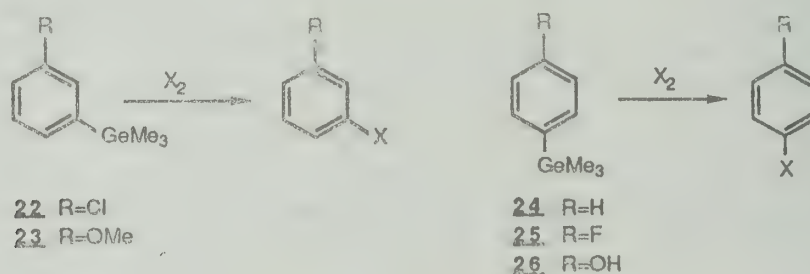
Aryl germanes have proven most useful in medicinal and radiopharmaceutical applications where the formation of a single radiohalogenated product is desired in order to avoid the need to separate isomeric mixture. Aryl silanes and aryl stannanes have been used for years to direct ipso-substitution of halogen into aromatic C-M bonds, however these reagents suffer various synthetic disadvantages. Silylated arenes generally require an electron donating substituents for halodesilylation yields to be high, and in rings active toward electrophiles, halodeprotonation products occur. Aryl stannanes give ipso-substitution

of the tin group on rings both activated and deactivated toward electrophiles, but the sensitivity of the C-Sn bond toward protolysis and alkaline hydrolysis reduces its usefulness.<sup>20</sup>

Germanium, which has a greater covalent radius and lower carbon-metal bond energy than silicon, is expected to be more susceptible to aromatic electrophilic substitution reactions than the analogous arylsilanes. In addition, since the C-Ge bond is four orders of magnitude less sensitive to acid hydrolysis than is the C-Sn bond, the utility of aryl germanes should be more general than the analogous tin arene.<sup>20</sup>

Moerlein has investigated the series of substituted aryl germanes shown in Scheme XI. Regiospecific incorporation of the halogen at the ipso position to  $\text{GeMe}_3$  with treatment of  $\text{X}_2$  was seen in all five substrates, with no products from competitive halodeprotonation observed. This was even true for compound **23** where, unlike the analogous arylsilane, substitution of the germanium moiety at the less reactive meta position occurs preferentially to electrophilic substitution at the activated ortho and para positions. This preference is attributed to the difference of the  $\text{ArC-Ge}$  and  $\text{ArC-H}$  bond energies, 74 kcal/mol and 110 kcal/mol, respectively, which makes halodegermylation the favored pathway in all cases, with ring substituents only affecting the rates of reaction. The rate of halogenation is also dependent on the halogenating species, as well as the solvent used. Yields and rates increase in the order  $\text{I}_2 < \text{Br}_2 < \text{Cl}_2$  for halogenating species and  $\text{CCl}_4 < \text{MeOH} < \text{AcOH}$  for solvents.<sup>20</sup>

Scheme XI

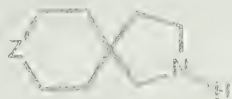


## BIOACTIVE GERMANES

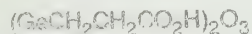
One of the first bioactive germanes was derived from the azaspiran moiety shown below, **27**. When  $\text{Z}=\text{CH}_2$ , the compound shows cytotoxic activity which increases with substitution at the "Z" methylene. Compounds with  $\text{Z}=\text{O}, \text{S}, \text{N}$  all showed decreased activity but,  $\text{Z}=\text{SiMe}_2$  gave enhanced activity, with good physiological compatibility. This led to investigation of the next IVB group element, germanium, with  $\text{Z} = \text{GeEt}_2$ .<sup>21</sup> This compound showed very low toxicity, and it has been used in the treatment of various cases of advanced carcinoma for up to three years with good results. It has also been shown to lower the blood pressure in dogs at relatively low dosages.<sup>21</sup>



Another bioactive germane is 2-carboxyethylgermanium sesquioxide (Ge-132), 28, which has antitumor activity, is an interferon inducer, and



27  $R = (CH_2)_4N(CH_3)_2$

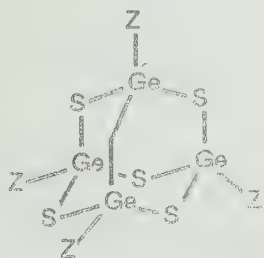


28 Ge-132

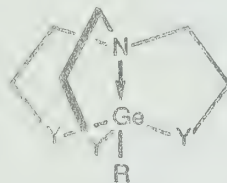
has almost no toxicity.<sup>22</sup> This compound has been shown by X-Ray crystallography to have a unique structure. It has an infinite sheet structure with the basic unit of the polymer being a 12-membered ring made up of six germanium tetrahedra bridged by oxygen atoms. The carboxylate chains are arranged alternately above and below the Ge-O network of the ring. The sheets are bonded together vertically by hydrogen bonds between carboxyl groups attached to each sheet.<sup>23</sup>

A related compound, germanium sesquisulfides 29, is prepared from the same 3-trichlorogermerylpropanoic acid or ester intermediate as Ge-132 related compounds. This compound exhibits the following unique bioactivity: It has greater antitumor activity in mice at lower dosages than Ge-132 and related sesquioxides; it shows strong action as a pain reliever, and has antioxidant activity.<sup>24</sup> The structure of this compound, confirmed by X-Ray crystallography,<sup>25</sup> is a bridgedhead germanium compound with highly symmetrical and stable adamantane structure having four germanium and six sulfur atoms per molecule.<sup>24</sup>

Another class of germanium compounds being investigated are the germatranes 30, which will be compared in bioactivity to analogous silatranes.<sup>26</sup> Bioactivity studies on these compound are currently being carried out.<sup>27,28</sup>



29  $Z = OR^1R^2CR^3HOX$



30  $Y = O, S$

## CONCLUSION

This review has presented some of the current uses of organogermanium compounds. In organic synthesis, germanium derivatives often have advantages over analogous silicon and tin reagents in stereo- and regiospecificity, as well as yield. Finally, certain germanium compounds have shown interesting bioactivity which warrant further study.

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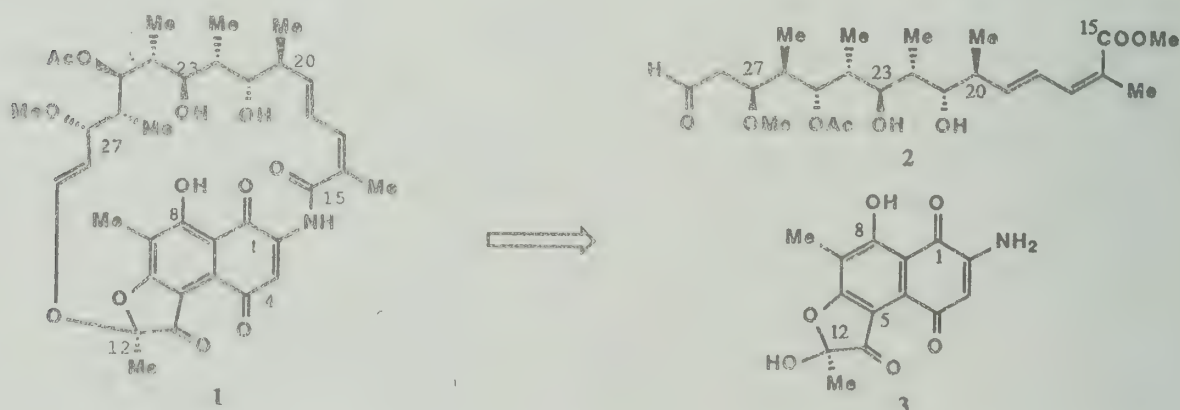
TOTAL SYNTHESIS OF RIFAMYCIN S; STEREOCONTROLLED SYNTHETIC  
APPROACHES TO THE ANSA BRIDGE

Reported by Kwang Jin Hwang

May 11, 1987

## INTRODUCTION

Rifamycins<sup>1</sup> are representatives of the ansamycins, which are characterized by an ansa (L. handle) bridge connecting two non-adjacent positions of an aromatic nucleus. These compounds are active against Gram-positive bacteria, and rifampicin, a rifamycin derivative, is an orally active antituberculous agent. Rifamycins were isolated as a complex mixture from the fermentation medium of *Nocardia mediterranei* by Sensi et al.<sup>2</sup> in 1959, and their structures were determined by chemical<sup>3</sup> and X-ray<sup>4</sup> analysis. Over the last ten years, the synthesis of rifamycin S 1 has attracted the interest of many organic chemists due to its biological activity and complex stereochemistry. Since Kishi's total synthesis of rifamycin S in 1980, several approaches to the synthesis of rifamycin S have been developed.



For the purpose of synthetic analysis, rifamycin S can be divided into a linear segment 2 and a naphthoquinone moiety 3 by disconnecting the two carbon-hetero atom bonds at C<sub>12</sub> and C<sub>15</sub>. The aliphatic portion of the linear segment (C<sub>20</sub>-C<sub>27</sub>) consists of a sequential array of alternating methyl and hydroxyl groups, corresponding to eight neighboring stereogenic centers, and there is a hidden C<sub>3</sub> symmetry element at C<sub>23</sub> if one considers only the C<sub>20</sub>-C<sub>26</sub>

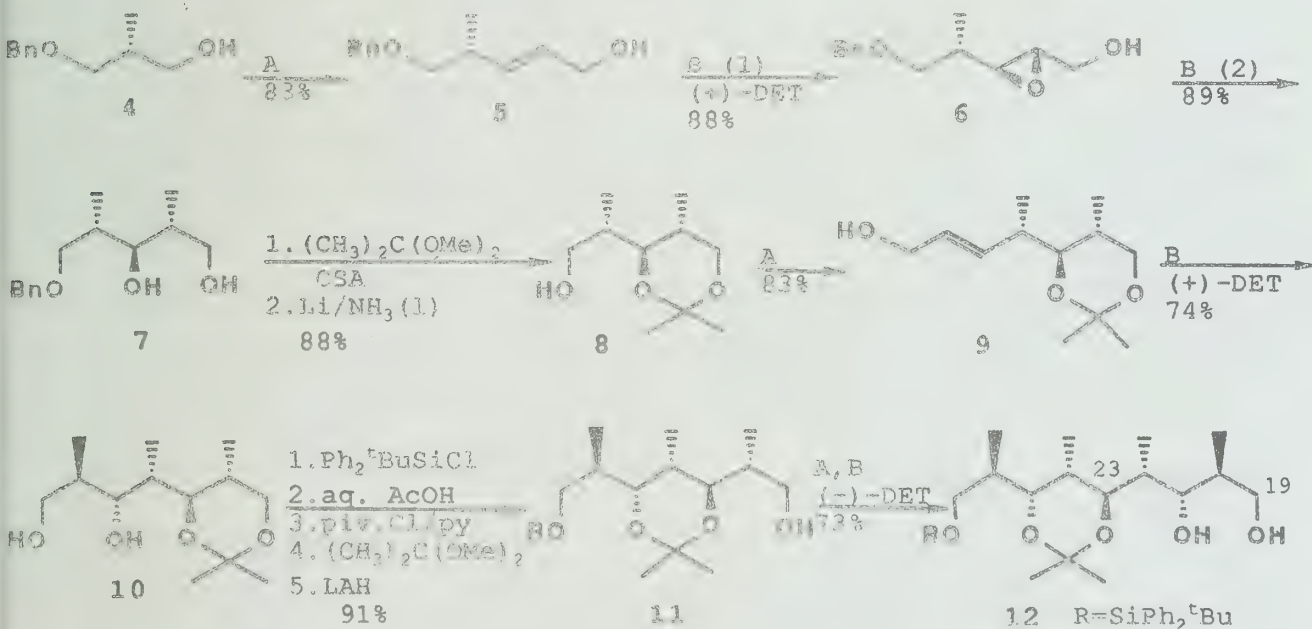


part. So far, most synthetic efforts have concentrated on generating the appropriate stereochemistry of the aliphatic portion of segment 2. Successful stereochemical control has derived from diverse methods,<sup>5-12</sup> including asymmetric epoxidation,<sup>5</sup> stereoselective hydroboration,<sup>6</sup> aldol condensation,<sup>7</sup> diene-aldehyde cyclocondensation,<sup>8</sup> and the use of a rigid bicyclic template.<sup>9</sup> The stereochemistry of the *trans*, *cis*-diene system in segment 2 has been controlled by a Wittig reaction or by temporary lactonization. The coupling of 2 and naphthoquinone moiety 3 was accomplished by using a modified aromatic derivative 51. In this report, these synthetic efforts will be described.

## SYNTHESIS OF THE ALIPHATIC SEGMENT (2)

### Asymmetric Epoxidation

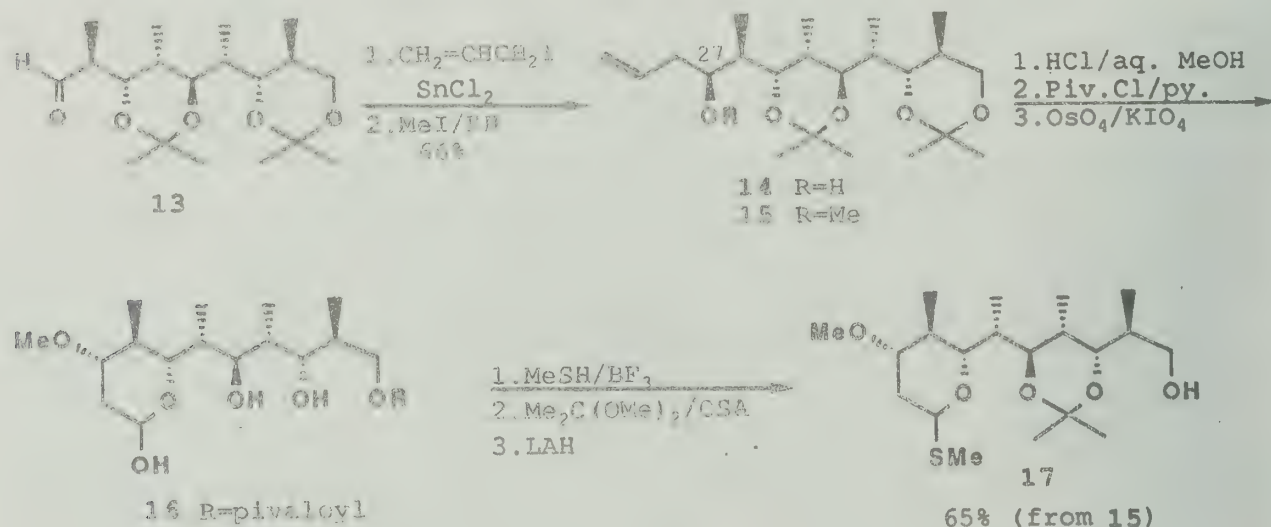
Kishi<sup>5</sup> utilized a Sharpless epoxidation<sup>13</sup> to control stereochemistry in the synthesis of segment 2. The optically active alcohol 4 was converted to the *trans* allylic alcohol 5 by Wittig reaction followed by Swern oxidation and DIBAL reduction. Epoxidation of the alcohol 5 using L-(+)-DET gave epoxide 6 with 95:5 overall stereoselectivity. Methylation of 6 with dimethyl cuprate proceeded regio- and stereospecifically to give the diol 7, which was protected



Method A: (1) (COCl)<sub>2</sub>/DMSO/Et<sub>3</sub>N; (2) (t-BuO)<sub>2</sub>P(O)CH<sub>2</sub>COOEt, t-BuOK; (3) DIBAL/CH<sub>2</sub>Cl<sub>2</sub>.

Method B: (1) <sup>t</sup>BuOOH, Diethyl tartrate, Ti(OPr<sup>i</sup>)<sub>4</sub>; (2) LiCuMe<sub>2</sub>, -40°/ether.

as an acetonide and debenzylated. A series of routine steps converted acetonide 8 to the trans allylic alcohol 9. Subsequent epoxidation and dimethyl cuprate addition gave the tetrol monoacetonide 10 with 95:5 overall stereoselectivity. After adjustment of protecting groups, the corresponding alcohol 11 was converted to the monoacetonide 12 by the same sequence of reactions, again with 95:5 stereoselectivity.



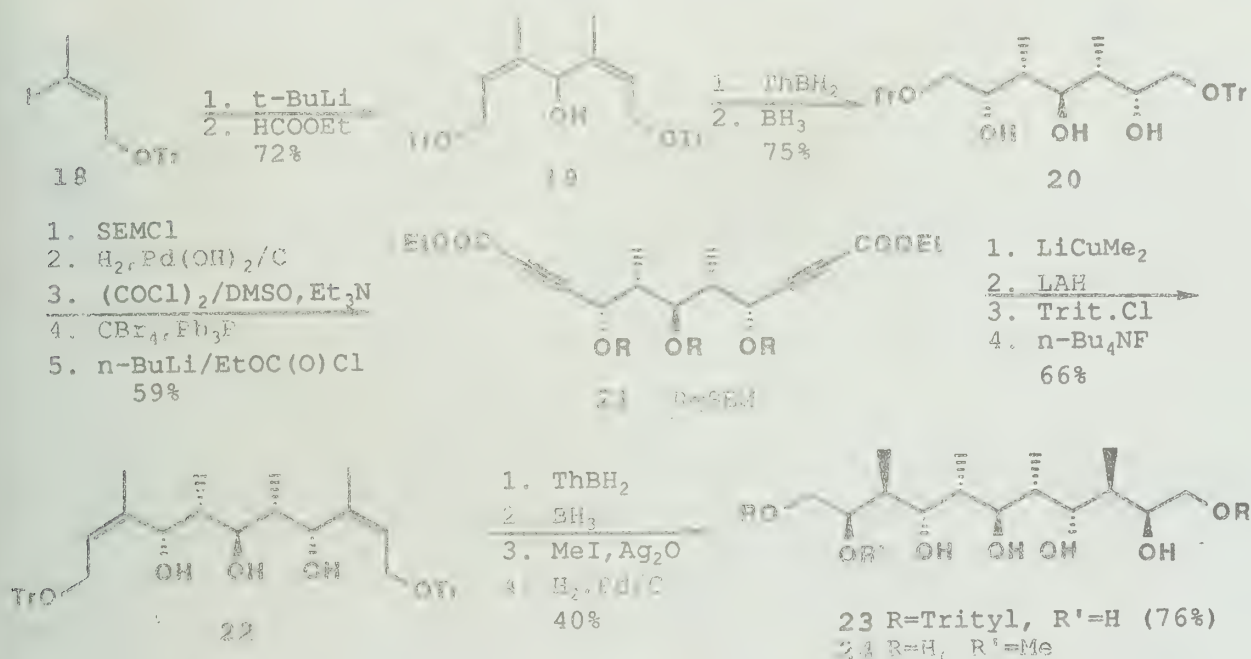
In order to control the stereochemistry at C<sub>27</sub> (rifamycin S numbering), acetonide 12 was converted to the aldehyde 13 and allowed to react with allyl tin<sup>14</sup> to give the desired alcohol 14 with a 20:1 stereoselectivity. Two of the hydroxyl groups in segment 2 (at C<sub>25</sub> and C<sub>27</sub>) are in masked form. The C<sub>27</sub> hydroxyl group in diacetonide 14 was differentiated by methylation. Differentiation of the C<sub>25</sub> hydroxyl group was accomplished by the formation of lactol 16, formed from 15 by selective protection of the primary alcohol, and the oxidative cleavage of the vinyl group. Finally, the hemithioacetal acetonide 17 was produced. The further elaboration of 17 into segment 2 is shown later.

#### Stereocentred Hydroboration

In 1983, Still<sup>6</sup> reported a synthesis of the aliphatic segment 24 of rifamycin S by two double hydroborations of bis-allylic alcohol intermediates, producing the four chiral centers of the two 1,3-diol units.

The first hydroboration substrate was the symmetrical bis-allylic alcohol 19, prepared from 2-butynol by Corey's hydroalumination/iodination reaction,

followed by tritylation, metallation, and addition to ethyl formate via 18. The sequential hydroboration of allylic alcohol 19 with thexylborane and borane gave the triol 20 as a 5:1 mixture with the undesired *d,l*-isomer. Triol 20 was converted to alkyne 21 by a sequence of reactions involving a Wittig reaction and an elimination to an acetylide that was trapped with ethyl chloroformate.



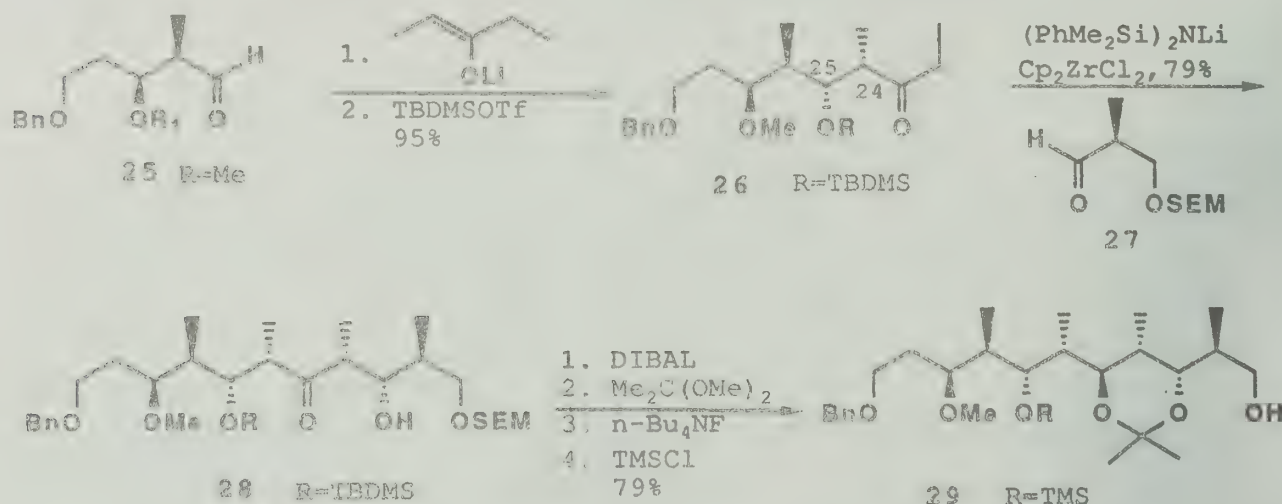
Alkyne 21 was converted to the bis-*cis* allylic alcohol 22 by a dimethyl cuprate addition, LAH reduction, tritylation, and deprotection sequence. Double hydroboration furnished the triol 23 as a 4:1 mixture of *meso*-23 and *d,l*-isomers. Mono-methylation of the less hindered hydroxyl group of 23 and catalytic detritylation gave 24, which has the correct stereochemistry at C<sub>20</sub> through C<sub>27</sub>. The complete ansa chain intermediate (C<sub>17</sub>-C<sub>19</sub>) was synthesized from 24 in ten steps by standard methods.<sup>9</sup>

#### Aldol Approach

Aldol reactions were utilized by Masamune to synthesize rifamycin S.<sup>7</sup> His approach started with optically active acid 25, prepared enantioselectively (99% ee) from 3-benzoyloxy-propanal by a boron-mediated aldol reaction, followed



by periodate cleavage.<sup>15</sup> To arrange the C<sub>24</sub> and C<sub>25</sub> stereochemistry, aldehyde 25 was reacted with the *Z*-enolate of 3-pentanone, giving the *syn* aldol product 26 with 20:1 stereoselectivity.



The *Z*-enolate of silyl ketone 26, which was generated by the bulky base 1,1,3,3-tetramethyl 1,3-diphenyldisilazide, was reacted with aldehyde 27 in the presence of *bis*-cyclopentadienyl zirconium dichloride<sup>16</sup> to give the *syn*-aldol product 28, establishing the configuration at C<sub>21</sub> and C<sub>22</sub> with an 8:1 diastereoselectivity. DIBAL reduction and a sequence of protective group alterations of ketone 28 gave alcohol 29, providing the C<sub>23</sub> stereochemistry with a 16:1 stereoselectivity.

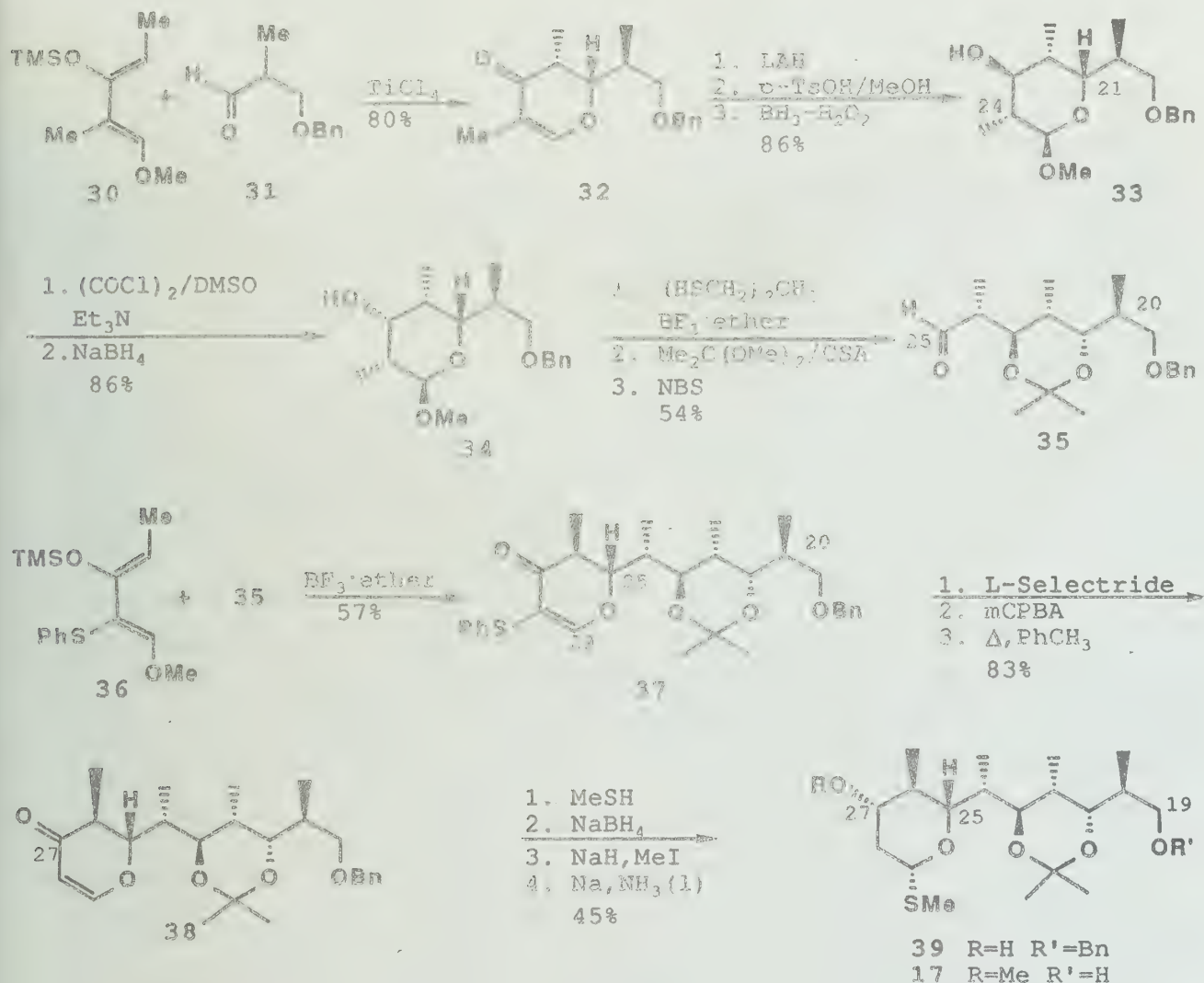
#### Diene-Aldehyde Cyclocondensation

Danishefsky<sup>8</sup> has recently reported a synthesis of the aliphatic segment 17 (Kishi's intermediate) based on the reiterative cyclocondensation of activated diene 30 with the appropriate aldehyde, in which the stereochemistry of the cyclocondensation adducts was remarkably controlled by the Lewis acid catalyst. Further selective chemical operations generated the chiral centers in a stereocontrolled manner.

The first step was the cyclocondensation of diene<sup>17</sup> 30 with aldehyde 31. In the presence of titanium tetrachloride, the *cis* adduct 32 was formed as a major product due to chelation control. Through the LAH reduction, Ferrier rearrangement, and hydroboration-oxidation, the ketone 32 was converted to



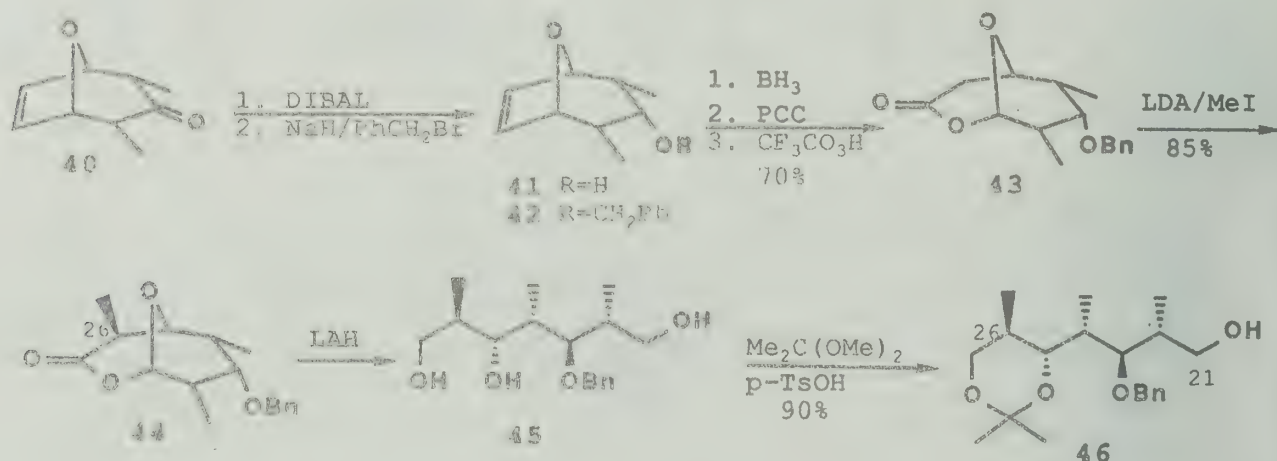
acetal 33, in which the correct stereochemistry of C<sub>24</sub> was established. The desired configuration at C<sub>23</sub> was inverted by a Swern oxidation followed by NaBH<sub>4</sub> reduction.



Thiolysis of the acetal, protection of the 1,3-diol, and dethiolation with NBS converted 34 into aldehyde 35, which was reacted with diene 36 under BF<sub>3</sub> catalysis (no chelation), to yield adduct 37 in a 4.5:1 (*trans/cis*) ratio. The phenylthio group in diene 36 was necessary to obtain the *trans* adduct in the BF<sub>3</sub>-catalyzed cyclocondensation.<sup>17</sup> After a conjugate reduction of 37 by L-selectride, oxidation and sulfoxide elimination afforded the dihydropyrone 38. The 1,4-addition of methanethiol followed by reduction produced the equatorial alcohol 39 stereoselectively (95:5). Subsequent methylation at C<sub>27</sub> and debenzylaton afforded the Kishi intermediate 17 as a racemate.

### Rigid Bicyclic Template

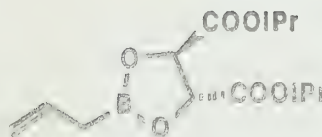
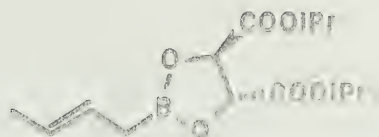
In 1985, Rama Rao<sup>9</sup> reported the synthesis of an aliphatic segment 46 utilizing bicyclic ketone 40 as starting material. The ketone was rigid enough to provide stereocontrolled functionalization and was also easily converted into an acyclic unit by the simple chemical operations.



The first step was a DIBAL reduction of ketone 40, prepared by cycloaddition<sup>18</sup> of furan and 2,4-dibromo-3-pentanone with Zn-Co catalyst, to give alcohol 41. The protected alcohol 42 was converted to lactone 43 through a sequence of reactions: hydroboration, PCC oxidation and Baeyer-Villiger reaction. *Exo*-preferred methylation of lactone 43 gave 44, providing the desired stereochemistry at C<sub>26</sub>. The alkylated lactone 44 was cleaved to the acyclic unit by treatment with excess LAH, and the two primary hydroxyl groups at C<sub>21</sub> and C<sub>27</sub> were differentiated by protecting one of them in the form of acetonide 46. Consequently, five contiguous stereogenic centers (C<sub>22</sub> to C<sub>26</sub>) were established by eight steps in 25% yield.

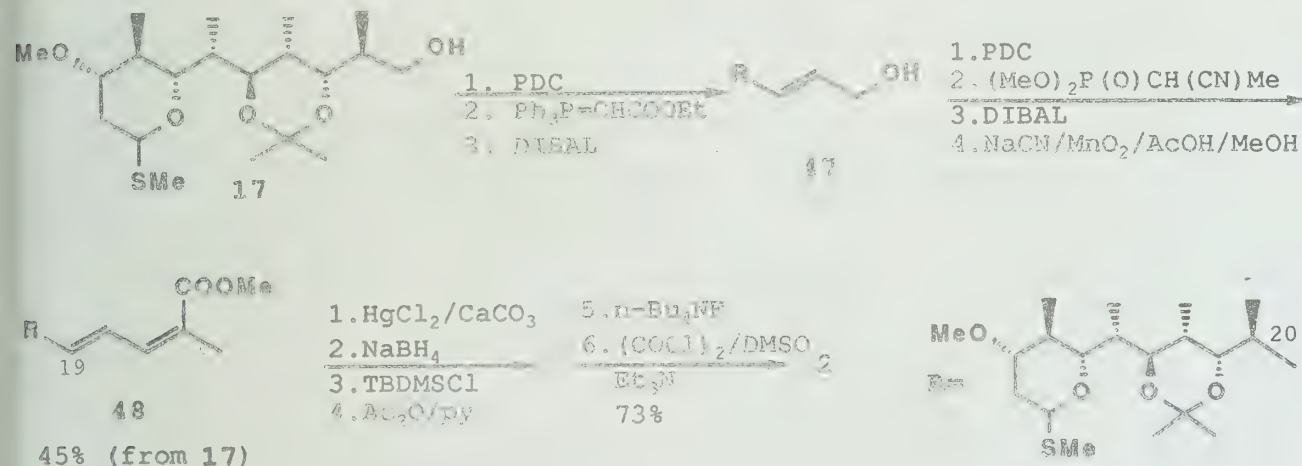
### Other Approaches

In addition to the methods described above, carbohydrates have been utilized by several groups<sup>10</sup> as starting materials for the synthesis of the aliphatic segment of rifamycin S. Roush<sup>11</sup> recently reported the synthesis of the C<sub>19</sub>-C<sub>29</sub> segment of rifamycin S using the chirally modified tartrate ester of the allylic boronate shown below.



### CONSTRUCTION OF THE TRANS, CIS-DIENE SYSTEM

Kishi utilized two Wittig reactions to construct the *trans*, *cis*-diene system ( $C_{16}$  to  $C_{19}$ ) of the segment 2. The *trans* double bond in 47 was smoothly introduced by a stabilized ylid. The *cis* double bond in 48 was formed by means of cyano Wittig reagent<sup>19</sup> with 10:1 stereoselectivity. Oxidative ring cleavage and reduction, adjustment of protecting groups, and Swern oxidation converted 48 into the desired aliphatic segment 2.



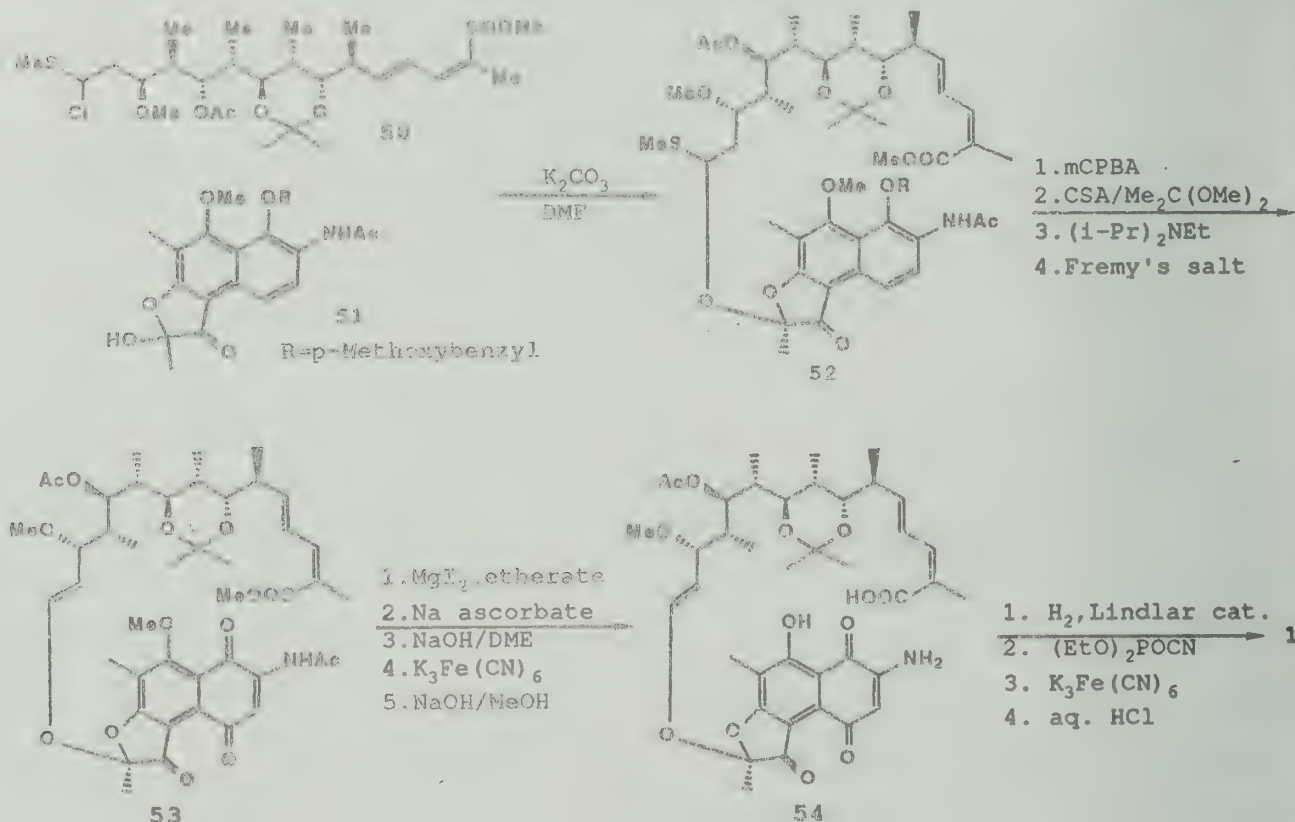
Another successful control of the *trans*, *cis* geometry was achieved by Masamune<sup>7</sup> using lactonization<sup>20</sup> of  $C_{19}$ -hydroxyl group and  $C_{15}$ -carbonyl group.

### ATTACHMENT OF THE ANSA BRIDGE TO THE AROMATIC MOIETY

The weak nucleophilicity<sup>21</sup> of the amine attached to the naphthoquinone ring prevented the formation of the amide bond. This problem was solved, however, by reducing the naphthoquinone to the quinol system. Another problem is tautomerization of the aromatic segment 3 at  $C_{12}$ . Based on a preliminary experiment,<sup>5</sup> Kishi modified an aromatic moiety 51, and avoided these problems. The aliphatic segment 50, derived from the chlorination of corresponding sulfide with N-chlorosuccinimide, was reacted with 51 to give diastereomer 52.



Sulfide oxidation, hydrolysis of *p*-methoxybenzyl ether, elimination of the sulfoxide, and then oxidation of the phenol with Fremy's salt gave 53. Through a sequence of reactions: demethylation with magnesium iodide<sup>22</sup>, reduction to quinol, hydrolysis of ester, reoxidation to quinone, and hydrolysis of amide, ester 53 was converted to acid 54. Finally, rifamycin S was formed by the following reactions: quinone reduction with Lindlar's catalyst, cyclization using DEPC (diethylphosphoryl cyanide) catalyst,<sup>23</sup> reoxidation to the quinone and hydrolysis of the acetonide.



## SUMMARY

The total synthesis of rifamycin S was completed by Kishi in many steps in low overall yield. His success, however, provided other challengers with a simpler intermediate target to approach. Five distinctive approaches to the stereochemistry in the aliphatic portion of segment 2 were reported: Masamune's aldol approach dramatically increased the yield (30% overall in only 18 steps) compared to Kishi's approach (45 steps, 4%); Danishefsky's diene-aldehyde approach was successful in preparing the Kishi intermediate 17 in 18 steps with 5% yield (Kishi: 33 steps, 8%); the double hydroboration approach by Still is a



remarkably efficient method that controlled the stereochemistry of four stereogenic centers in one step.

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# ORGANIC SEMINAR ABSTRACTS

1987-88, SEMESTER I

University of Illinois

SCHOOL OF CHEMICAL SCIENCES

DEPARTMENT OF CHEMISTRY

UNIVERSITY OF ILLINOIS

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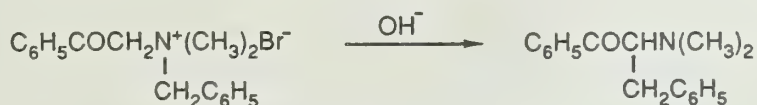
# PHOTO-STEVENS REARRANGEMENT OF SULFONIUM YLIDES

Reported by Jian-Jian Zhang

Sept. 14, 1987

In 1928 Stevens and co-workers<sup>1</sup> found that treatment of phenacylbenzyl-dimethylammonium bromide with base provides a high yield of 2-dimethylamino-3-phenyl propiophenone. This transformation has come to be generally known as the Stevens rearrangement.

Scheme I.

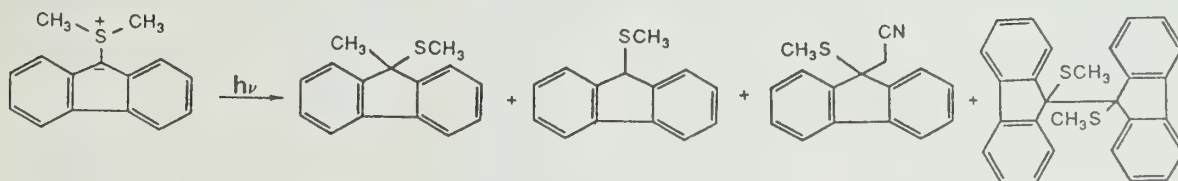


Subsequent research has shown that the base catalysed thermal Stevens rearrangement proceeds through an intermediate ylide, and that the reaction can be extended to sulfonium and phosphonium compounds.<sup>2</sup> It has been shown that the rearrangement occurs with retention of configuration on the migrating group<sup>3</sup> and appears to be intramolecular.<sup>4</sup> The mechanism of the Stevens rearrangement has been carefully investigated by isotope labelling,<sup>5a</sup> CIDNP effects,<sup>5,6</sup> stereochemical probes<sup>5a</sup>, and solvent viscosity studies.<sup>5b</sup> The conclusion has been made that homolysis of a carbon-heteroatom bond to form a neutral radical pair is the critical initial step in this process.

In contrast to the thermal Stevens rearrangement of sulfonium ylides, the photoinduced rearrangement of sulfonium ylides is surprisingly rare because of their susceptibility to photocleavage of the dipolar sulfur-carbon bond to give products derived from carbene and ketene intermediates.<sup>7</sup> In 1986 Griller and co-workers<sup>8</sup> reported that photolysis of diazofluorene in acetonitrile solvent in the presence of dimethyl sulfide gives Stevens rearrangement product, presumably by secondary photolysis of the first formed ylide.

The orbital symmetry requirements for rearrangement of electronically excited species are precisely opposite those of the corresponding ground states. We studied the mechanism of the photo-Stevens rearrangement of 9-dimethylsulfonium fluorenylide; its irradiation gives the Stevens rearrangement product by a dissociative mechanism. An alternative path considered first by Lepley has a single-electron oxidation of the ylide as

Scheme II.



the key initial step.<sup>9</sup> This process yields a radical cation which could rearrange to give the characteristic Stevens product. This possibility was considered again more recently by Radom and co-workers who calculated theoretical reaction paths for some ionized ylides which they call "ylidions."<sup>10</sup> Their findings suggest that the prototype sulfonium ylidion ( $\text{H}_2\text{SCH}_2^+$ ) exists in a potential minimum and will not spontaneously rearrange. In our case the one electron oxidation to the ylidion does not initiate this reaction.

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ACTIVE TRANSPORT ACROSS MEMBRANES MEDIATED BY SYNTHETIC  
IONOPHORES

Reported by Rajgopal Srinivasan

September 28, 1987.

### Introduction

Organic chemists, particularly in the last two decades, have been involved in an attempt to mimic biological phenomena. The growing importance of this field is evidenced by the ever-increasing number of publications and conferences being held.<sup>1</sup> An area that is being actively investigated concerns transport of hydrophilic substances such as ions across a lipophilic membrane. The lipophilic membrane surrounding a cell acts as a selectively permeable layer preventing diffusion of hydrophilic molecules into the cytoplasm. However for the normal functioning of cells certain ions such as  $\text{Na}^+$ ,  $\text{K}^+$ , etc., have to be maintained in the cytoplasm within narrowly defined concentration ranges. This is accomplished by the transport systems. One mode of transport termed active transport involves movement of an ion across a membrane and across its electrochemical gradient. Such movement is often accompanied by co-transport of another species along its concentration gradient in the same or opposing direction. This report will focus on the techniques organic chemists have employed to realize active transport in artificial systems. The objectives behind these investigations have been to understand the various factors involved in transport processes and to reveal possible applications in analytical chemistry and separation science.

### Design of Ionophore

A synthetic ionophore must possess certain characteristics to function in an efficient manner. The complex formed by the carrier with the ion should be stable, but not too stable. An optimal  $K_a$  of  $10^5$ - $10^6 \text{ M}^{-1}$  is desirable.<sup>2</sup> Additionally, the carrier must exist in at least two different conformations, one with a high affinity and the other with very low affinity for the ion. Further the transition from one conformer to the other must be easily achieved.

### Proton Driven Transport Systems

The inspiration to design ionophores driven by a proton gradient has been largely derived from naturally occurring antibiotics capable of demonstrating active transport. One such antibiotic, monensin, can specifically transport  $\text{Na}^+$  from a basic aqueous medium to an acidic aqueous medium through an organic layer, against a concentration gradient.<sup>3</sup>

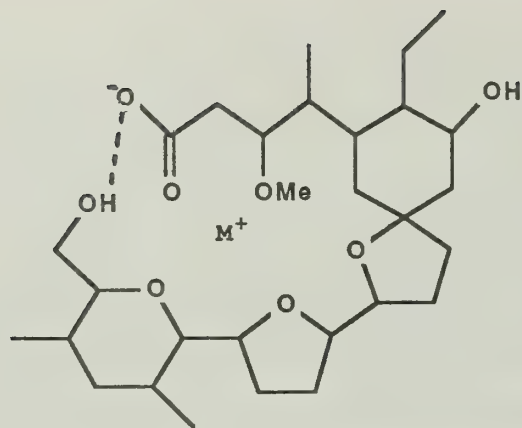
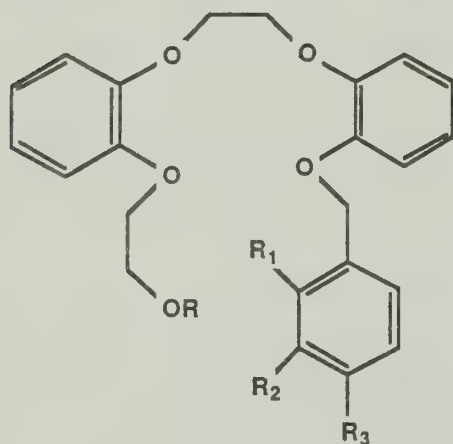


Figure 1

Monensin consists of a terminal hydroxyl and a terminal carboxylic group. In basic medium the carboxylate anion can form a hydrogen bond with the hydroxyl hydrogen to produce a cyclic structure which can trap a  $\text{Na}^+$  ion to form a lipophilic complex (Figure 1). The lipophilic complex can then diffuse across the organic layer to the acidic layer where neutralization occurs resulting in loss of the cyclic structure and hence, release of  $\text{Na}^+$ . In an attempt to mimic monensin, molecules containing terminal hydroxyl and carboxylic groups have been designed.



- 1  $\text{R}=\text{R}_2=\text{R}_3=\text{H}$ ,  $\text{R}_1=\text{COOH}$
- 2  $\text{R}=\text{R}_1=\text{R}_3=\text{H}$ ,  $\text{R}_2=\text{COOH}$
- 3  $\text{R}=\text{R}_1=\text{R}_2=\text{H}$ ,  $\text{R}_3=\text{COOH}$
- 4  $\text{R}=\text{Me}$ ,  $\text{R}_1=\text{COOH}$ ,  $\text{R}_2=\text{R}_3=\text{H}$

Figure 2

Table 1 shows the data for compounds 1, 2, 3 and 4. Molecule 1, which is capable of forming the required cyclic structure, is not only able to transport ions actively across the organic phase, but is also selective towards  $\text{K}^+$  ions. On the other hand 2 and 3 cannot form a cyclic structure and hence not only do they not form a complex with the ion, but are also not lipophilic enough to be taken up by the organic layer. Hence, they show no transport whatsoever. In the case of 4, while transport is observed, selectivity is much lower. While the lipophilicity of 4 enables it to carry ions across an organic layer, its inability to form a cyclic structure prevents it from doing so selectively.



Table 1. Ion transporting ability of 1,2,3 and 4.

Ionophore	Transported Cation (%)		Total (%)
	Na <sup>+</sup>	K <sup>+</sup>	
1	13	60	73
2	0	0	0
3	0	0	0
4	28	41	69

The experimental scheme is shown below:

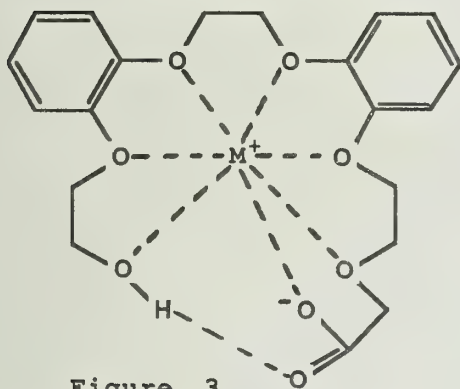
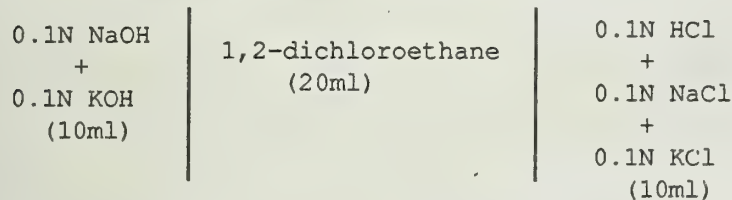
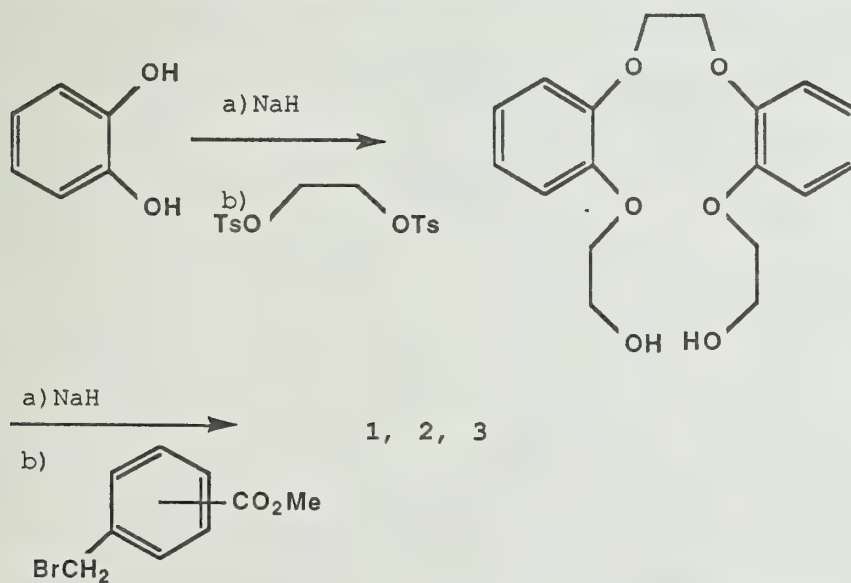
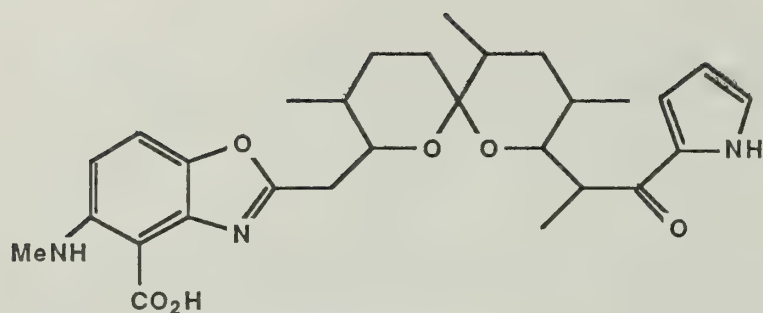


Figure 3

Compounds 1-3 were synthesized as follows:

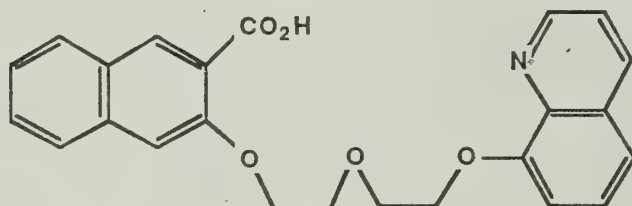


One of the best known Ca<sup>2+</sup> ionophores is an antibiotic called A23187, in which a pyrrole and a 8-carboxybenzoxazole ring are the terminal groups.<sup>5</sup>

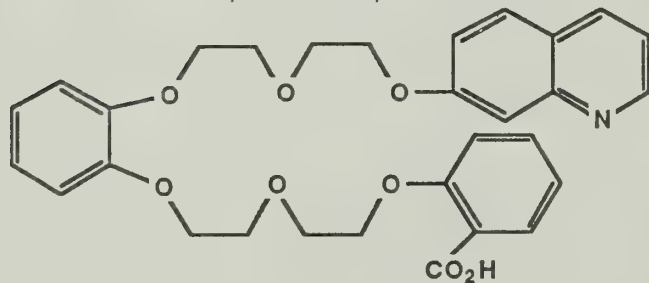


A23187

A number of compounds, incorporating carboxylic and quinoline termini in their structure, have been synthesized.<sup>6</sup>

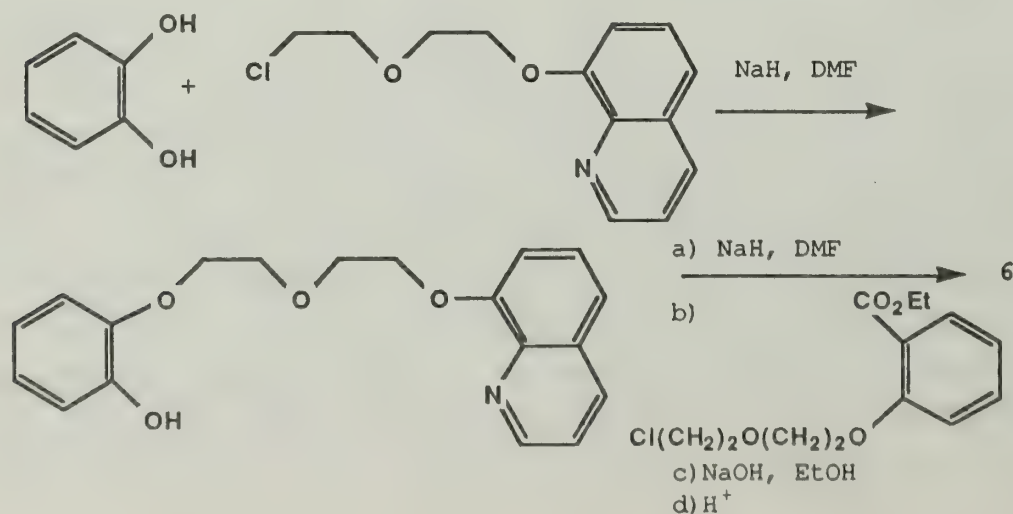


5a n=1, 5b n=2, 5c n=3



6

The above ionophores were examined for their ion transporting ability across a chloroform layer. The ionophores transport ions actively as well as selectively. Thus, 5a, b and c are specific towards  $\text{Li}^+$ ,  $\text{Na}^+$  and  $\text{K}^+$  respectively. Ionophore 6 is selective towards  $\text{K}^+$ . The synthesis of 6 is outlined below.



## Light Driven Transport Systems

Nature uses light as a trigger for various processes such as vision, photosynthesis, etc. Shinkai and others realized that light could be used to bring about a change in conformation of an ionophore if it had a suitably functionalized photoantenna built into it.<sup>7</sup> Thus, molecules containing a diazo functionality were synthesized. The compounds are so designed as to have a coordinating group on both nitrogens. In the cis form, both the coordinating groups are proximate and favor stronger complexation than in the trans form, where the groups are removed from one another.

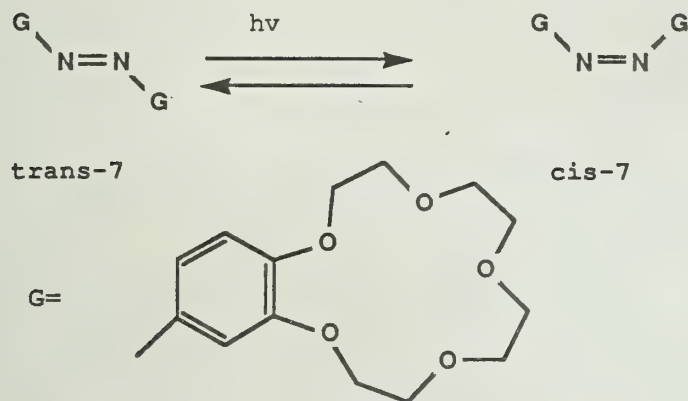


Figure 5

By varying G, in principle, any desired ion can be complexed. This ionophore has been employed to demonstrate active transport in a system such as the one depicted in figure 6.

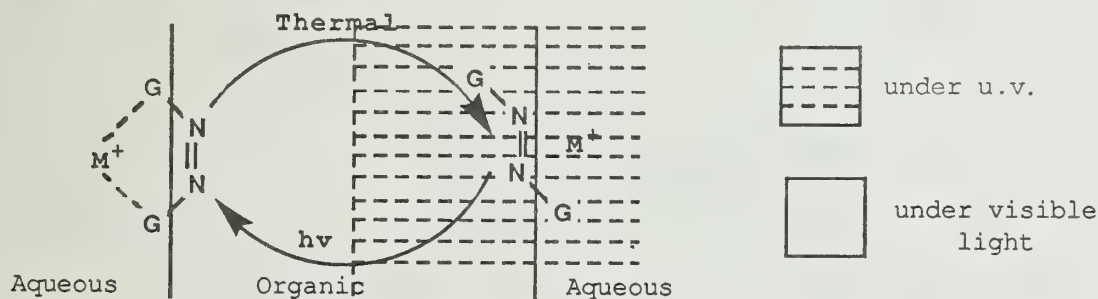


Figure 6

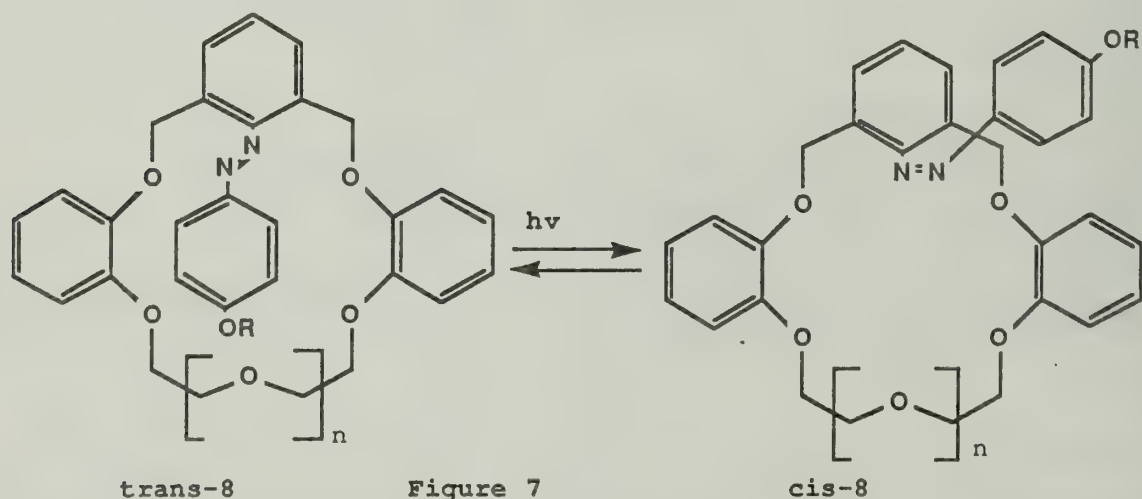
In the region under u.v. light, the metal ion is complexed but when the complexes diffuse to the region not under the influence of u.v. light the complex breaks down to release the ion. It has been shown by Shinkai that, while the cis isomer is soluble in aqueous medium the trans isomer is not, due to a difference in polarity. The ability of trans-7 and cis-7 to extract metal cations from an aqueous phase to an organic phase have been examined and the results are given in table 2.

Table 2. Extraction of methyl orange salt of alkali metals

Ionophore	Alkali metal extracted			
	Na <sup>+</sup>	K <sup>+</sup>	Rb <sup>+</sup>	Cs <sup>+</sup>
trans-7	29.6	1.3	29.3	24.1
cis-7	5.3	55.2	68.8	36.2

The data indicate that while the trans isomer is selective towards Na<sup>+</sup>, the cis isomer prefers K<sup>+</sup>. This can be easily rationalized on the basis of a size argument. The 15-crown-5 ether can accommodate a Na<sup>+</sup> ion, but not a K<sup>+</sup> ion. So, each of the crown ethers present in the molecule complex a Na<sup>+</sup> ion to form a 2:1 (ion/ionophore) complex. In the case of the larger K<sup>+</sup> ion, which cannot fit in the cavity of the 15-crown-5 ether, the cis isomer can form a sandwich type 1:1 complex and can consequently extract larger ions better.

More recently,<sup>8</sup> another diazo ionophore has been developed (Figure 7). The trans isomer of 8 has an intra-annular substituent in the form of a phenyl ring. On photoirradiation to the cis form, the intra-annular substituent is removed making room for an ion to occupy the ensuing cavity. Furthermore, one of the nitrogens can also act as a coordinating site. So, the cis form should exhibit a high binding constant.



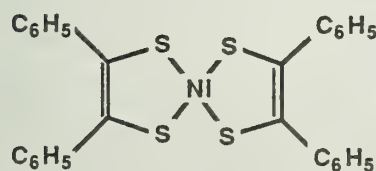
The ion complexing abilities of 8 have been examined, and the following facts have emerged. The trans isomer does not extract any Na<sup>+</sup>, while the cis isomer does. However, interestingly, the trans form can in fact extract larger metal ions such as K<sup>+</sup>, Rb<sup>+</sup> and Cs<sup>+</sup>. The ionophore shows absolutely no affinity for Li<sup>+</sup>. To explain the differing behavior of the trans isomer, it has been postulated that with smaller ions complexation is of the "nest-in" type, while for larger ions it is of the "perch-on" variety.



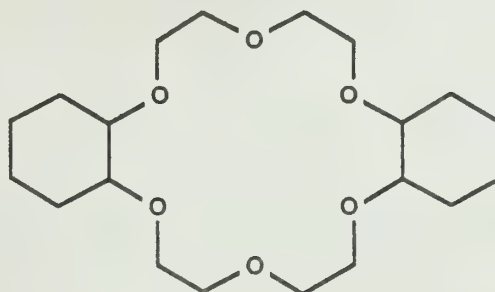
Ion transport studies were carried out with **8** ( $n = 2$ ). However, the ionophore has been examined for passive transport only, and is a very likely candidate for active transport studies. Since the metal ion is complexed in an "all-or-nothing" fashion, further investigations could lead to a series of photocontrollable membranes.

### Redox Switched Crown Eters

Grimaldi and Lehn<sup>9</sup> reported an artificial system in which alkali metal ions, coupled to a simultaneous flow of electrons in the same direction, were transported across an organic layer containing an electron carrier and a cation carrier.



9



10

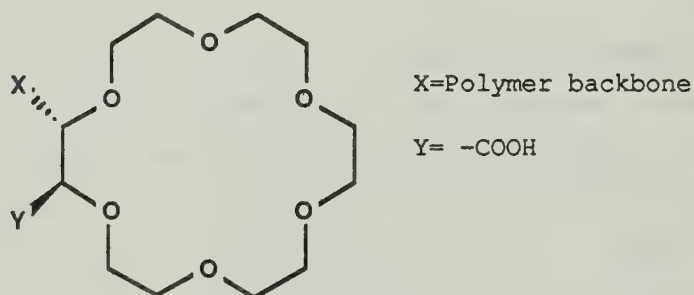
They employed **9**, nickel bisdithiolene, as the electron carrier and **10**, dicyclohexyl-18-crown-6, as the ion carrier. In their experiment an organic phase containing **9** and **10** was used to separate two aqueous phases, one containing a reducing agent (potassium dithionite) and the other an oxidizing agent (potassium ferricyanide). The reducing agent converts  $\text{Ni}^0$  to  $\text{Ni}^{-1}$ , and **10** complexes  $\text{K}^+$ , to form a double complex ion pair  $\{(\text{9-Ni}^{-1})(\text{10-K}^+)\}$ . The ion pair diffuses across to the phase containing the oxidizing agent, where  $\text{Ni}^{-1}$  is converted to  $\text{Ni}^0$  releasing  $\text{K}^+$  simultaneously. This is followed by diffusion back of the empty macrocycle and **9** to the reduction phase. Active transport of  $\text{K}^+$  was thus achieved. The transport rate is cation dependent and is much slower for  $\text{Na}^+$ . Thus, the above system incorporates a redox pump, a selection process and regulation. Manabe<sup>10</sup> and co-workers have also reported a redox carrier with two thiol groups (reduced form), which can be oxidized to a cyclic di-sulfide.

### Transport of Amino Acids Across a Membrane

There are in the literature a few reports<sup>11,12,14,15</sup> where amino acids have been transported against a gradient. Two of the reports describe transport of an amino acid anion against its gradient, with the simultaneous diffusion of  $\text{K}^+$ , mediated along its gradient, by a  $\text{K}^+$  specific carrier. Selection of amino acid anion is based in the differing hydrophobicities of the anions, with the more hydrophobic anions being transported faster.

## Transport Through a Polymer Membrane

This report has thus far concentrated on transport across liquid membranes. However, in natural systems matters are very different. Transport in natural systems occurs via channels containing specific ion recognition sites. This could be mimicked by suspending a series of ionophores along a polymer backbone, so that the ion could actually hop from one site to another. Fyles and co-workers suspended crown ethers bearing a carboxylic group from a backbone derived from acryloyl chloride (11).<sup>13</sup> Films of the polymer were not strong enough to be used as membranes themselves, and were therefore incorporated into Teflon filters to provide the required strength. The membrane was placed in a glass vessel and used to partition an aqueous acidic phase from an aqueous basic phase. In the basic phase the carboxylate anion was formed, enabling complexation of the ion. The ion then hopped from one crown ether to the other, with the concomitant transfer of protons in the opposing direction. In the acidic region, neutralization of the carboxylate anion resulted in release of the cation.



11

## Summary

As can be seen from the material presented a considerable effort has been expended in designing novel ionophores and employing them to demonstrate active transport. These efforts have resulted in a better understanding of transport phenomena in biological systems. However much remains to be done. A more thorough analysis of the transport data is required. Chemists have not spent as much time analysing the results as they have in making newer ionophores. Furthermore, most of the attempts have been directed at transport of ions, and very little data is available in the literature on efforts regarding transport of neutral molecules which is quite common in biological systems. The available data should however go a long way in developing efficient separation techniques and in areas such as ion-selective electrodes.

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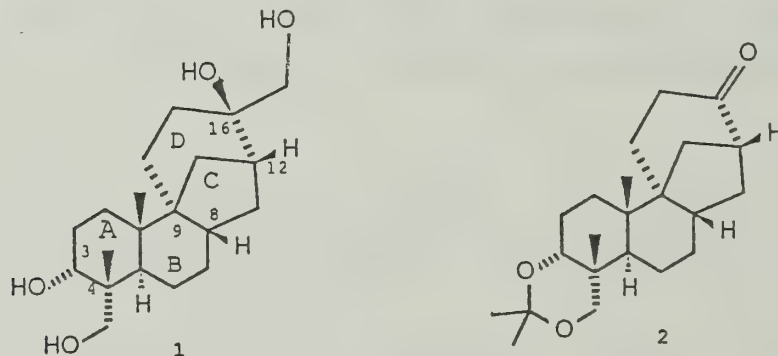
# TOTAL SYNTHESIS OF APHIDICOLIN

Reported by Kwok Yee

October 5, 1987

## Introduction.

The tetracyclic diterpene aphidicolin 1 was isolated in 1972 by Hesp and co-workers from the fungus *Cephalosporium Aphidicola* Petch.<sup>1</sup> The structure of this novel tetracyclic tetraol was first assigned by Hesp<sup>2</sup> through degradation and spectroscopic analysis<sup>2</sup> and was confirmed by X-ray analysis.<sup>1</sup> Hesp proposed that the parent hydrocarbon be called aphidicolane.<sup>2</sup> Despite its simple functionality, aphidicolin exhibits striking antibiotic<sup>3</sup> and antitumor<sup>4</sup> activities via as a selective inhibition of DNA polymerase  $\alpha$  and as a potential anticancer compound.<sup>5</sup>



Biosynthetic investigations by Bu'Lock<sup>6</sup> in 1975 revealed the diterpenoid origin of the carbon skeleton. Hanson's recent work on the labelling pattern of aphidicolin biosynthesized from  $[1-^{13}\text{C}]$  and  $[2-^{13}\text{C}]$  and  $[1,2-^{13}\text{C}_2]$  acetates defines the constituent isoprene units. The appearance of a  $2\text{H}-^{13}\text{C}$  coupling in the NMR spectrum of material biosynthesized from  $[4-^2\text{H}_2, 3-^{13}\text{C}]$  mevalonic acid established that a hydrogen atom had migrated from C-9 to C-8 during the formation of aphidicolin.<sup>7</sup>

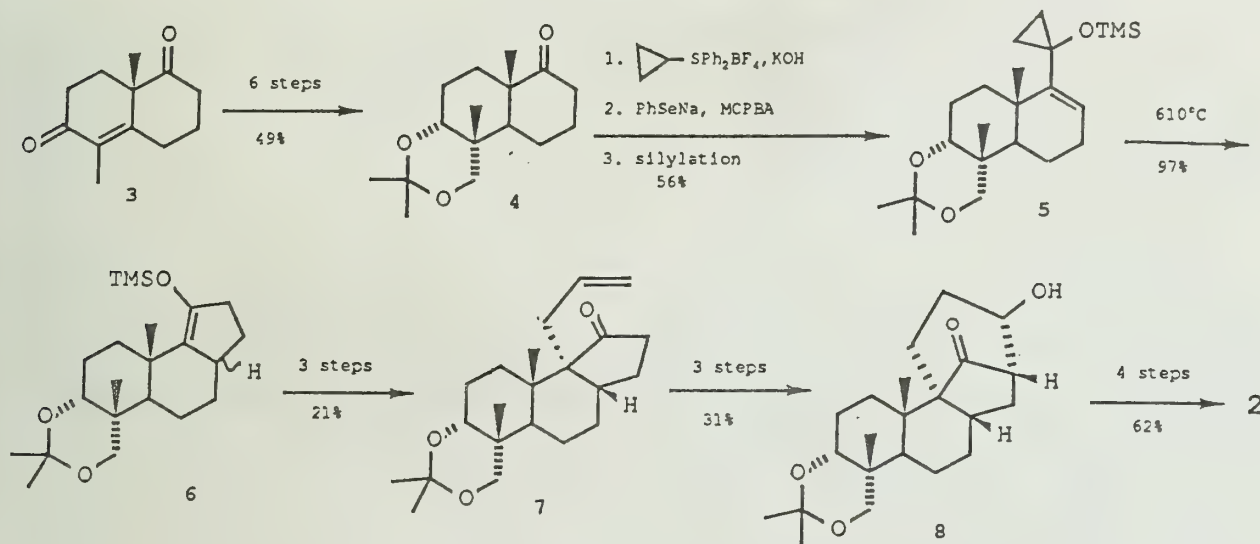
The synthesis of aphidicolin 1 has attracted many organic chemists<sup>8</sup> owing to its biological activity and unusual structure. Because the keto acetone 2 has been obtained from, and reconverted into, aphidicolin 1,<sup>2</sup> compound 2 became the synthetic target in many total syntheses of 1. Since the first total syntheses of 1 were independently reported by Trost<sup>9</sup> and McMurry<sup>12</sup> in 1979, several approaches have followed and can be grouped into the following five categories on the basis of the methods used to construct the bridged C and D rings: (1) internal aldol condensation, (2) direct organometallic carbonylation, (3) internal  $\alpha$  alkylation, (4) photolytic ring contraction, and (5) solvolytic rearrangement.



# Internal aldol condensation.

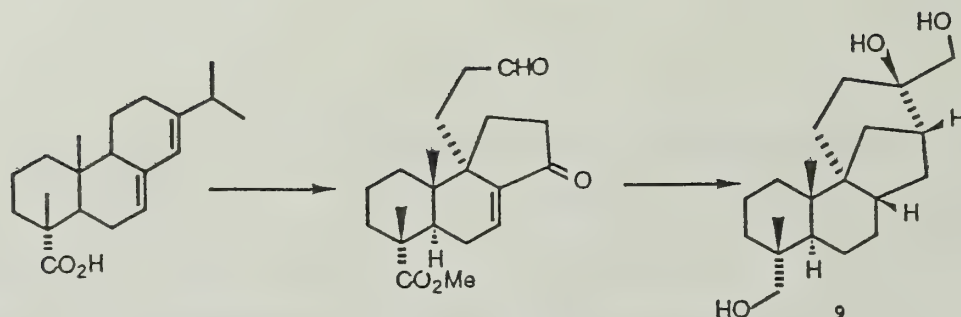
Trost<sup>9</sup> synthesized the bicyclo[3.2.1]octane system (C/D ring) of 1 by the internal aldol condensation method starting with dione 3 (Scheme I). After reductive formylation of 3 was achieved, selective hydride reduction followed by deketalization and acetonide formation gave ketone 4. Condensation of ketone 4

Scheme I



with diphenylsulfonium cyclopropylide under reversible conditions yielded an oxaspiropentane intermediate which was then converted to the crystalline alkylidenecyclopropyl ether 5 by selenide ring opening and elimination. Thermal rearrangement of 5 via flash vacuum pyrolysis gave 6 as a 2:1 mixture of epimers at C-8. The major isomer was assigned the 8 $\alpha$  configuration. The epimeric mixture was converted to a single enol silane having the correct stereochemistry at C-8 by oxidation with Pd(OAc)<sub>2</sub> followed by lithium-ammonia reduction. Alkylation of the corresponding enolate with excess allyl iodide gave 7. Hydroboration-oxidation followed by PCC oxidation gave the aldehyde which under basic conditions underwent an aldol-type cyclization to form 8. Wolf-Kishner reduction of 8 afforded an alcohol which was oxidized to give 2 and a total synthesis of aphidicolin was then completed.

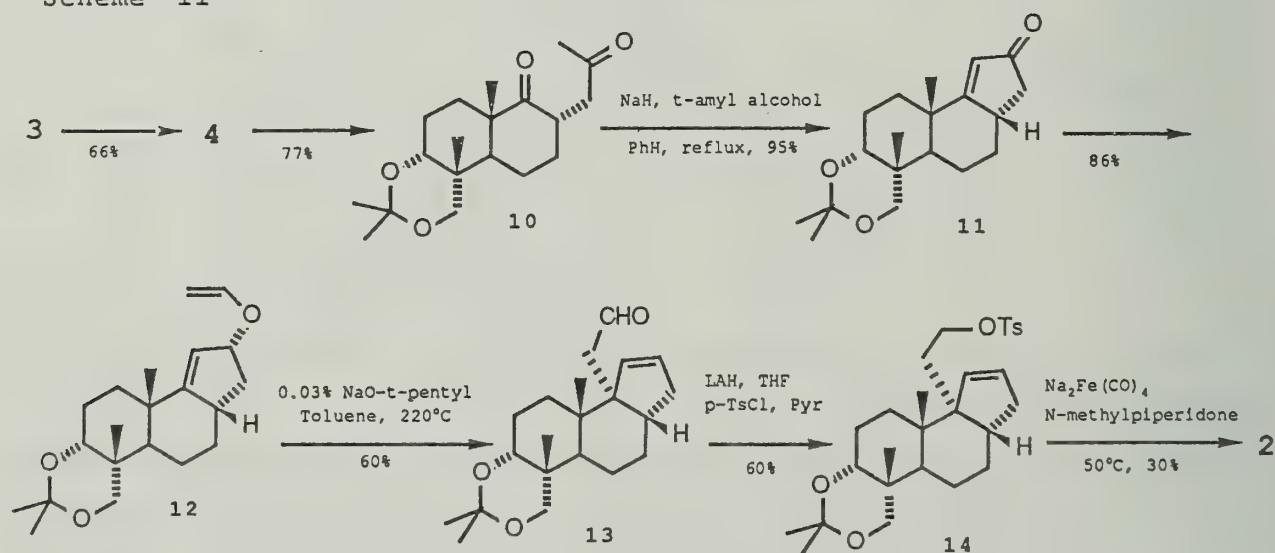
Ohno<sup>10</sup> has also reported an enantioselective synthesis of the aphidicolin analog 3-deoxyaphidicolin, 9, using the internal aldol condensation method.



### Direct Organometallic Carbonylation:<sup>11</sup>

The first example using  $\text{Na}_2\text{Fe}(\text{CO})_4$  ("Collman's reagent") in natural product syntheses was accomplished by McMurry<sup>12</sup> who utilized this reagent to construct the D-ring of aphidicolin 1 (Scheme II). The synthesis started with 3 which was converted to 4 in 66% yield using a procedure similar to Trost's<sup>9</sup>. Alkylation

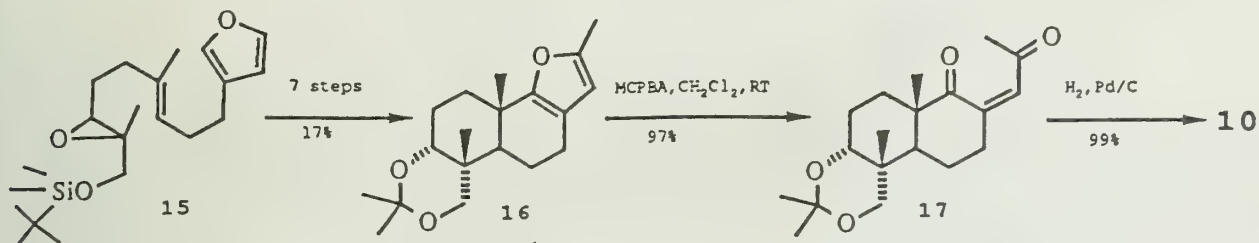
Scheme II



of 4 with methallyl iodide followed by cleavage of the olefinic bond afforded dione 10 which then underwent internal aldol cyclization to give the key intermediate 11. Stereospecific reduction of 11 with LAH resulted in a single alcohol and the Claisen rearrangement of its vinyl ether 12 was carried out in the presence of a small amount of strong base to give 13 in good yield. After the reduction of 13 and subsequent tosylation, the unsaturated tosylate 14 was carbonylated with disodium tetracarbonyl ferrate yielding a crystalline ketoacetone 2 in 30% yield after column chromatography.

A concise formal total synthesis of **1** via diketone **10** was reported by Tanis<sup>13</sup> in which a furan-terminated, epoxide-initiated cationic cyclization of **15** was involved (Scheme III). The crucial step in this approach was the oxidation of **16** with MCPBA to give the unsaturated diketone **17** which could be further hydrogenated to **10**.

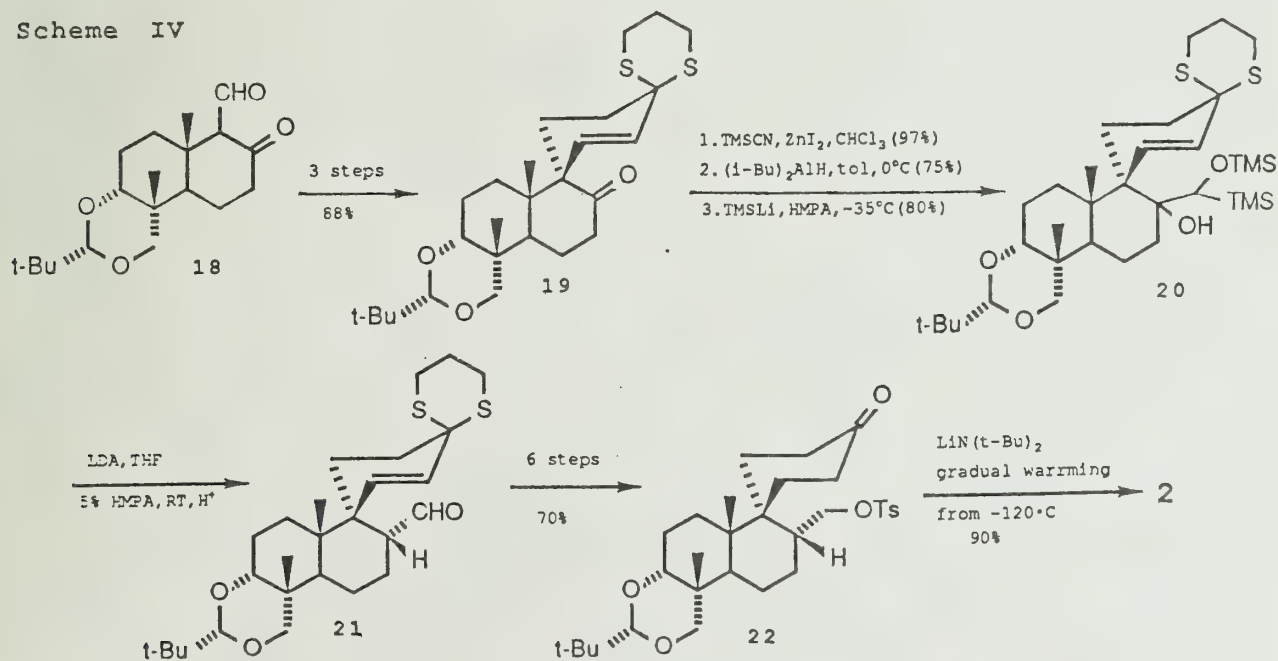
Scheme III



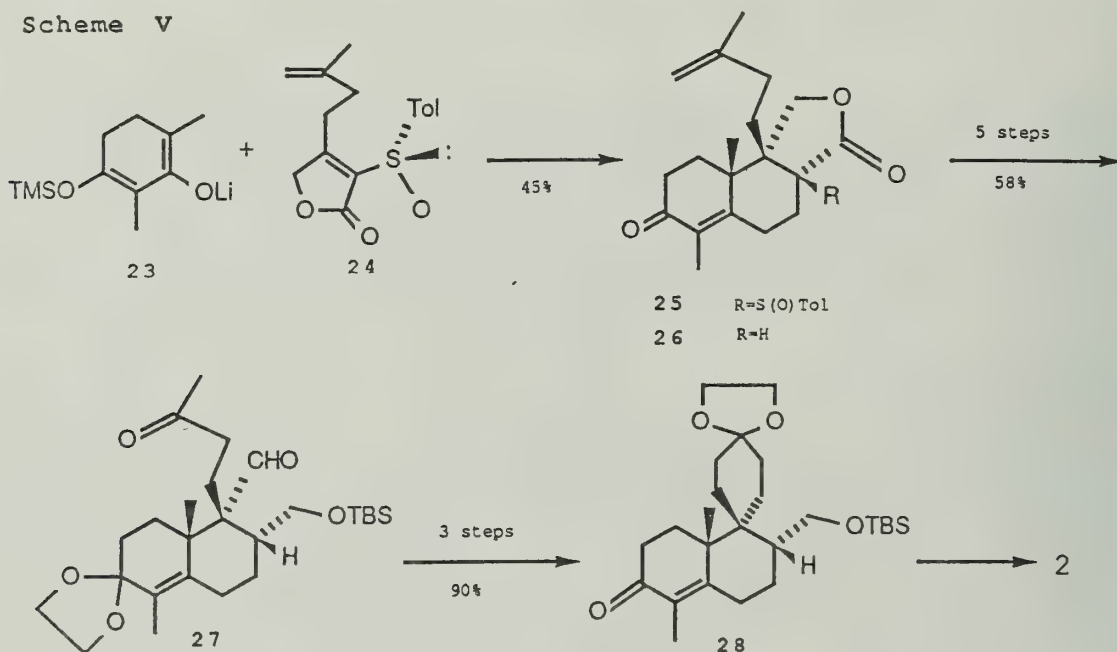
### Internal $\alpha$ alkylation.

A total synthesis of **2** was reported by Corey<sup>14</sup> utilizing an internal  $\alpha$  alkylation of the spirocyclic ketone **22** to form the C/D ring system of **1** (Scheme IV). The keto aldehyde **18**<sup>14</sup> underwent Michael addition and Robinson annulation to give the spirocyclic diketone **19**. The synthetic sequence converting **19** to **21** proved to be a general solution to the problem of attaching a carbon to very hindered ketonic groups. The synthesis of **2** was best achieved by kinetic enolization of **22** with a highly hindered base at low temperature which favored the desired alkylation at C-12.

Scheme IV



Holton<sup>15</sup> has recently achieved the first enantioselective total synthesis of 1 in which the key step involved the chirality transfer via a kinetic Michael addition of lithium dienolate 23<sup>16a</sup> to (S)-(+)-sulfinyl butenolide, 24<sup>16b</sup> (Scheme V). Selective ozonolysis of the disubstituted olefin was followed by



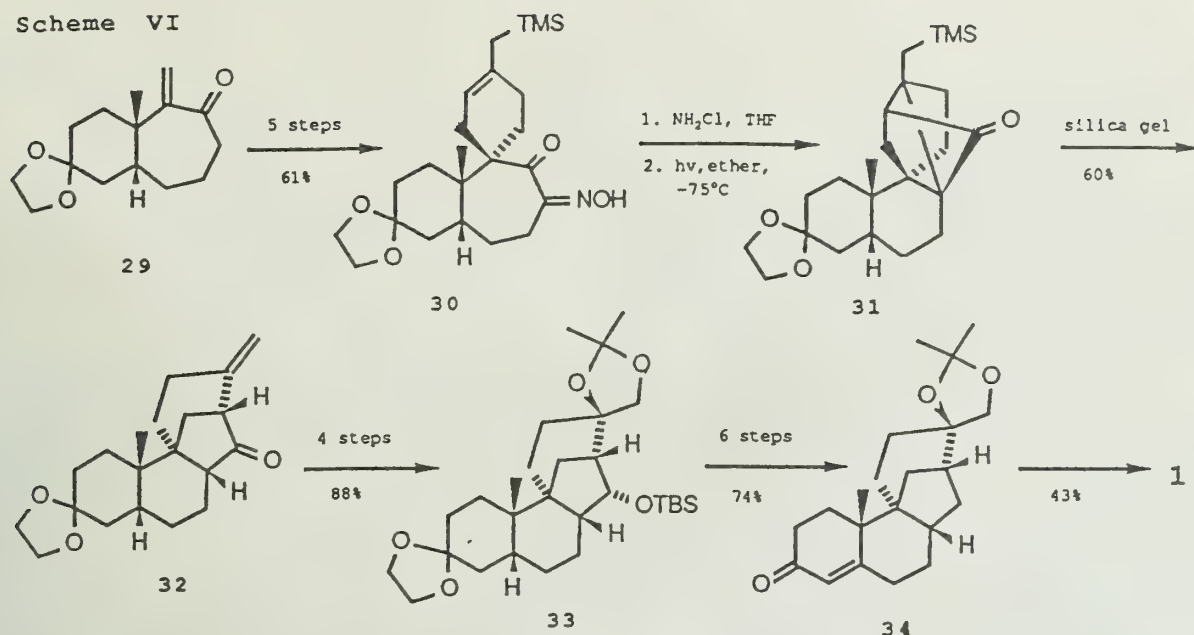
reduction, selective silylation and oxidation to produce the keto aldehyde 27. Construction of the D-ring by aldol condensation followed by selective hydrogenation gave 28 which was similar to Corey's key intermediate 22. Enone 28 was then converted to 2 using Corey's methodology for A/B ring construction. All products of the reaction sequence from 24 were optically active and the resulting product 2 had an optical rotation identical to that of the natural product.

#### Ring Contraction.

The unique steps in the total synthesis of 1 by Ireland<sup>17</sup> are the process of the spiroannulation of the  $\alpha$ -methylene ketone 29<sup>18</sup> followed by B-ring contraction and solvolysis to establish the bicyclo[3.2.1]octane C/D ring structure.<sup>19</sup> The key oximino ketone intermediate 30 was obtained from 29 in 5 steps. Photolysis of the diazo ketone formed from the oximino ketone 30 gave the butanone 31 as the sole product. The rearrangement of 31 to 32 occurred during silica gel chromatography yielding the B/C/D rings with correct stereochemistry. Reduction of ketone 32 afforded the C-13  $\alpha$ -oriented alcohol which was converted to the tert-butyldimethylsilyl ether. The bulky silyl group



Scheme VI

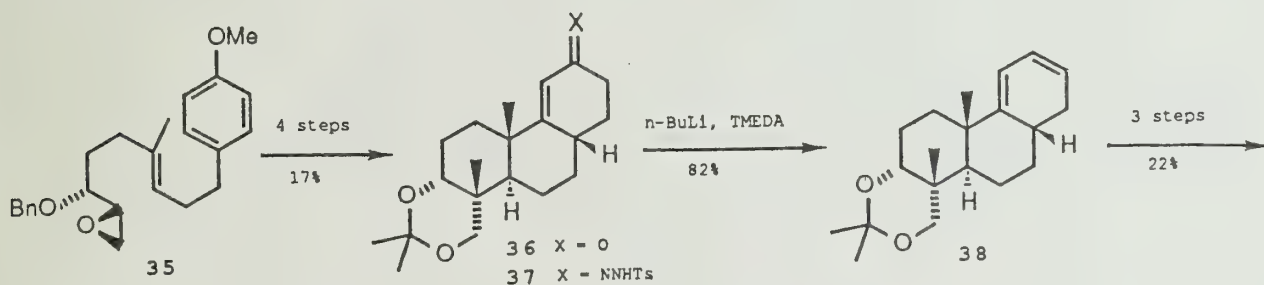


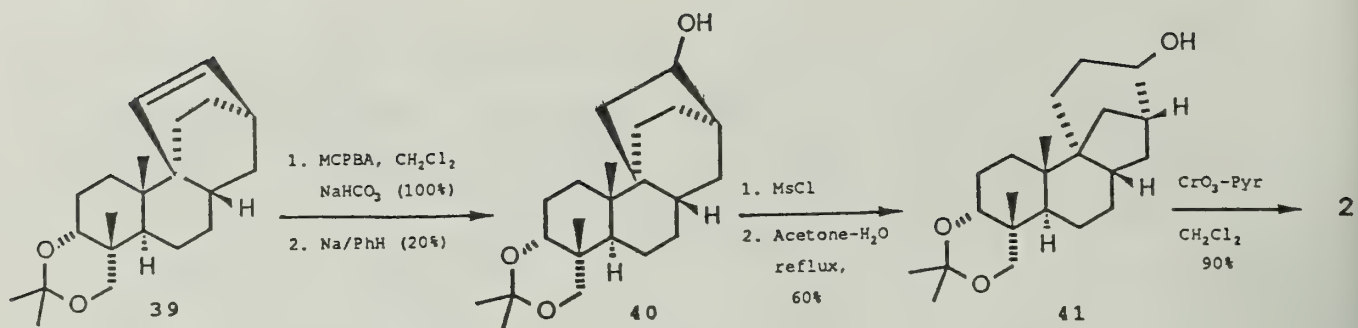
served to block the  $\alpha$ -face of the double bond, and osmylation took place stereospecifically to give the desired diol which was readily protected as the acetonide 33. The cis A/B ring junction was transformed to the desired trans-isomer through the formation of the  $\alpha,\beta$ -unsaturated ketone 34. Subsequent  $\alpha$ -methylation and methoxylation of 34 yielded the ketone which was then stereospecifically reduced to give the final product 1.

#### Solvolytic Rearrangement.

Van Tamelen<sup>20</sup> successfully utilized solvolytic rearrangement of bicyclo[2.2.2]octanol 40 to form the C/D ring system of 1 (Scheme VII). Biogenetic-type cyclization of 35 resulted in the formation of the A/B ring with the desired stereochemistry and subsequent Birch reduction gave the  $\alpha,\beta$ -unsaturated ketone 36 which could be converted to cyclohexadiene 38 through a Bamford-Stevens-type reaction. After a Diels-Alder reaction between the cyclohexadiene 38 and maleic anhydride, bicyclo[2.2.2]octene 39 was obtained

Scheme VII

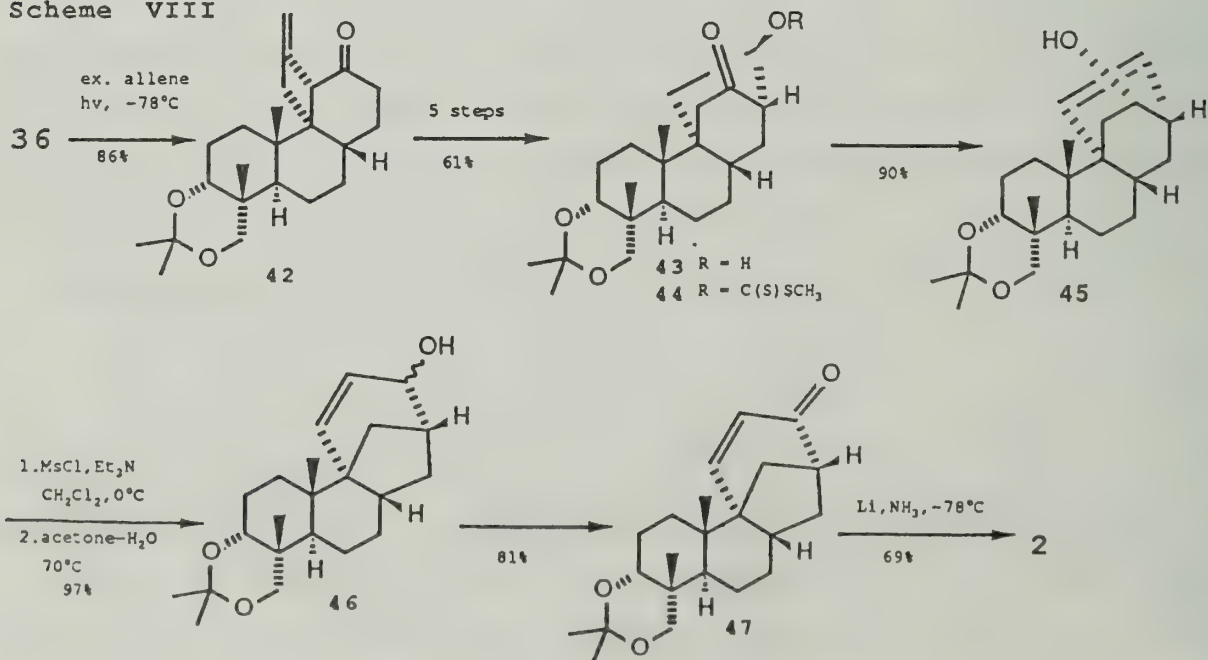




after the catalytic reduction and oxidative bis-decarboxylation. Epoxidation of 39 followed by reduction afforded the bicyclo[2.2.2]octanol 40. Solvolytic rearrangement of 40 took place by refluxing in acetone- $\text{H}_2\text{O}$  mixture generating the bicyclo[3.2.1]octanol 41 which was easily transformed into 2.

Bettolo<sup>21</sup> used a similar strategy which took advantage of a solvolytic rearrangement of [2.2.2]octenol 45 (Scheme VIII). Photoaddition of the  $\alpha,\beta$ -enone 36 with allene afforded a single adduct 42. After ketalization, oxidative cleavage of the olefinic bond followed by reduction of the resulting ketone gave cyclobutanol which was converted to bicyclo[2.2.2] hydroxyoctanone 43 by a retro-aldol opening and re-cyclization. After the reduction of the ketone and formation of the double bond via 44, bicyclo[2.2.2]octenol 45 underwent solvolytic rearrangement to give bicyclo[3.2.1]octenol which was transformed to 2 through enone 47.

Scheme VIII



## Summary.

In addition to its important biological properties, aphidicolin has served as a challenging target molecule to synthetic organic chemists. Seven total syntheses of 1 have been divided into five categories. Holton's approach is believed to be the best to date, not only because the synthesis is enantioselective, but also because it achieved the highest overall yield (12% from (S)-(+)-sulfinyl butenolide, 24). Other interesting approaches to 1 which are still under development have been reported in the literature.<sup>8,22</sup>

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IS PI DELOCALIZATION DESTABILIZING?

Reported by David Hartsough

October 15, 1987

The concept of aromaticity has played a central role in the history of organic chemistry. Although it has always been an ill defined and ambiguous concept it has served organic chemists well. The main feature of aromaticity theory is the notion that aromatic systems owe their stabilization, however defined, to the gain in energy due to pi bond delocalization. Recent theoretical work has cast some doubt upon this idea. The purpose of this seminar will be to examine the results of these theoretical studies and to see what they have to tell us about our present understanding of aromaticity.

Prior to embarking upon a discussion of present theories of aromaticity it should prove helpful to achieve some historical perspective concerning aromaticity.

Benzene was first isolated in 1825 by Faraday and later by decarboxylation of benzoic acid by Mitscherlich in 1834. In 1865 Kekule proposed two structures for benzene and a rapid bond shift interconverting them and rendering all six carbons equivalent.<sup>2</sup> At this time, Kekule also began to use the terms "aromatic" and "aromaticity" to describe structural features of benzenoid compounds. Shortly thereafter, Erlenmeyer began the now accepted practice of basing a molecule's admittance to the class of aromatics upon its reactivity.<sup>1</sup>

In 1890 Eugene Bamberger postulated that an aromatic molecule required six "potential valencies" in a "hexacentric array". Although Bamberger's notion of "potential valencies" did not take hold his idea of six as the "magic" number was raised again 35 years later.<sup>3</sup> In 1925 Robinson promoted the idea of the aromatic sextet. Robinson noted that many compounds possess both aromatic character and a sextet of electrons which one cannot assign to particular positions in the molecular structure.

Hückel, in 1932, postulated the  $4n+2$  rule which states that planar monocyclic systems containing  $4n+2$  pi electrons would exhibit aromatic stabilization.<sup>4</sup> A later addition to this rule goes on to state that the corresponding  $4n$  pi electron systems would be destabilized and should possess the property of anti-aromaticity.<sup>5</sup> These rules were formulated on the basis of Hückel Molecular Orbital (HMO) theory.

HMO theory is a crude, simplified form of Molecular Orbital theory. In HMO theory it is assumed that the sigma framework does not interact with the pi electron system above and below it.

Calculation of pi electron energies are made through use of secular equations of the type shown in equation (1).

$$\sum C_r (H_{rs} - S_{rs} E) = 0 \quad \text{Eq. (1)}$$

These equations give rise to the secular determinant. Further approximations are made to aid in solution of the secular determinant. The first of these is that the overlap integral,  $S_{rs}$ , is by definition 0 when  $r \neq s$  and 1 when  $r = s$ , where  $r$  and  $s$  denote the carbon atoms in question. Additionally it is assumed that the resonance integral,  $H_{rs}$ , which is a measure of the binding power of the bond  $rs$ , is 0 except when  $r$  and  $s$  are nearest neighbors (e.g.  $H_{14} = 0$ ,  $H_{12} \neq 0$ ). The determinant can then be readily solved and the roots obtained provide the energy levels of the pi MO's.

Energies of localized versus delocalized systems can also be calculated. Taking benzene as an example, its secular determinant is solved and the energies of the MO's obtained. These energy levels are then compared to those calculated for a single Kekule structure of benzene in which the double bonds are not allowed to interact. The calculated pi energies are then compared between the interactive and the non-interactive models. The difference between the two is the resonance energy. Unfortunately utilization of this reference structure yields favorable resonance energies for both  $4n$  and  $4n+2$  electron systems. It does predict greater stabilization for the  $4n+2$  systems versus the  $4n$  systems but this difference diminishes as  $n$  increases.<sup>7</sup>

An alternative reference would be the acyclic polyene. Furthermore, it was suggested that the Resonance Energy Per Electron (REPE) would serve as a useful measure of stabilization for comparison of systems containing different numbers of pi electrons. These methods were employed by Schaad and Hess and predicted that  $4n$  annulenes would possess negative resonance energies and the  $4n+2$  annulenes would have positive resonance energies. This method also states that as  $n$  increases the difference in energy between the  $4n$  and  $4n+2$  systems diminishes and at high  $n$  both types of systems will become non-aromatic.<sup>8</sup>

Criteria for aromaticity other than calculation of resonance energies have also been suggested. The most widely used method is observation of diatropicity in the  $^1\text{H}$  NMR spectrum. Use of diatropicity is based on the idea that aromatic stabilization and the increase in diamagnetic susceptibility are both a result of the same interactions of pi electrons. This theory states that the susceptibility caused by an induced ring current is proportional to the square of the ring area multiplied by the resonance energy due to that ring.<sup>9</sup> Another criterion that is often used is  $\Delta H$  of hydrogenation. In this method the heat of hydrogenation of the aromatic system is compared with the heat of hydrogenation of an equivalent number of

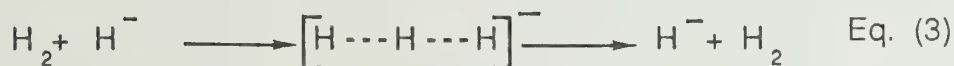
ethylene units. The amount by which  $\Delta H_{\text{hyd}}$  of the resonating system is lowered compared to the expected value, based upon the isolated double bonds, is the resonance stabilization.<sup>10</sup>

The above criteria as well as others, such as first and second order double bond fixation<sup>11</sup> and various graph theories,<sup>12</sup> have been used to assess the degree of aromaticity in chemical systems. The survey above is not intended, however, to convey the idea that aromaticity is some physical property that can be easily measured.

Due to the variety of theories, many molecules have been encountered which are classified as aromatic by one theory but non-aromatic by another. Because of this situation Heilbronner has stated that "the amount of confusion caused by the term 'aromaticity' in the student's mind is not compensated for by gain in the understanding of the chemistry and physics of molecules so classified...aromaticity cannot be measured, it is not a physical quantity...and it is not an observed one."<sup>13</sup> Lloyd has also been critical of the use of the term aromaticity saying "...it would be better if the term aromatic were discontinued...and that it should pass with other technical terms which have outlived their usefulness into the realm of the historian of chemistry."<sup>14</sup>

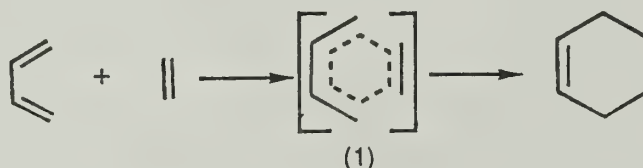
The controversy briefly mentioned above was one of the problems Epiotis wished to deal with in his development of the Unified Valence Bond Theory of Electronic Structure. The form of Valence Bond (VB) theory espoused by Epiotis was meant to be used in a fashion similar to HMO theory, that is to make simple qualitative predictions. Epiotis notes the two following formal drawbacks of HMO theory: 1) That it neglects interelectronic coulomb repulsion and internuclear coulomb repulsion. 2) That it neglects coulomb attraction between an electron on one center and the nuclei of other centers. These limitations lead to several instances in which HMO theory effectively "breaks down."<sup>15</sup>

One example of this breakdown is that HMO theory is unable to properly predict the ordering of electronically excited states. In the case of 1,3-butadiene HMO theory predicts the "singly excited"  $\pi_1^2$ ,  $\pi_2^1$ ,  $\pi_3^1$  state to be of lower energy than the "doubly excited"  $\pi_1^2$ ,  $\pi_3^2$  state by a significant margin. However SCF-MO-CI calculations show the order of the two states to be reversed.<sup>16</sup> Another instance in which HMO theory fails, and also a significant instance for the discussion at hand, is its predictions regarding the degenerate hydrogen bond exchange shown in equations (2) and (3).





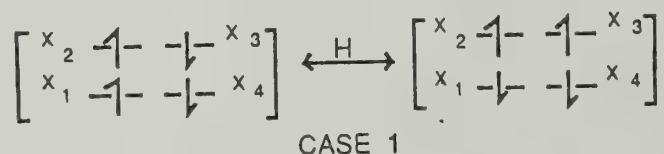
HMO theory would predict both delocalized structures to be energy minima. SCF-MO-CI calculations on the other hand predict both to be transition states. Some credence is lent to the SCF-MO-CI calculations by the observation that in the case of butadiene and ethylene (1) is a transition state and not a stable complex.<sup>17</sup>



Lastly, some experimental and computational evidence disagree with HMO theory when it predicts that a thermally allowed reaction proceeds through a symmetrical transition state.<sup>18</sup>

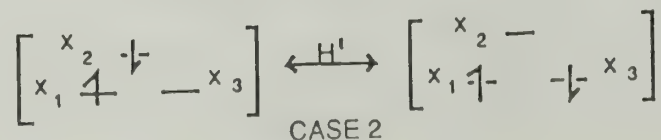
The cause of these shortcomings in HMO theory can be detected by examination of the equivalent level of VB theory. Hückel Valence Bond (HVB) theory is the VB equivalent of HMO. Accordingly all of the assumptions utilized in formulating HMO are present in HVB.

At the HVB level one can imagine four major types of electron delocalization or electron localization as expressed by the matrix interaction element  $H_{ij}$ . The first case is one in which  $H_{ij}$  connects two Configuration Wavefunctions (CW) which describe the same orbital occupancy (Case 1).



This type of mixing is termed electron localization.

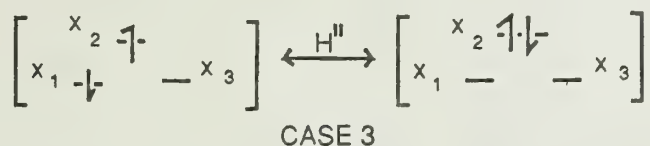
The next case has  $H_{ij}$  connecting two CW's which differ by one occupied spin orbital (Case 2).



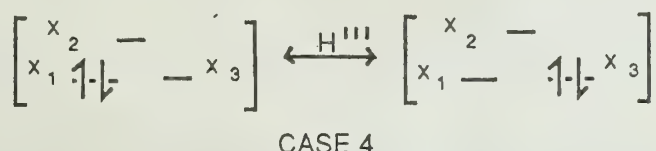
This is termed covalent delocalization.



The third case is ionic delocalization and involves two CW's interacting which again differ by one spin orbital but which no longer conserve the number of singly occupied AO's (Case 3).



Finally bielectronic ionic delocalization is possible and in this instance  $H_{ij}$  expresses the interaction shown below (Case 4).

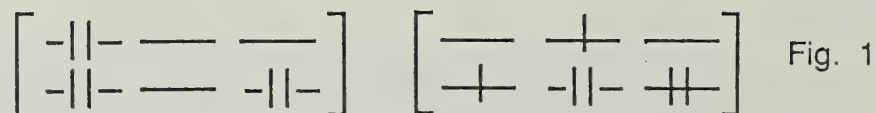


As a result of the assumptions outlined earlier i.e. neglect of exchange and coulomb correlation, HVB produces unrestrained "ionic" delocalization. This is due to an artificially small E and an overlap integral of zero. This type of interaction, given by  $H''$ , is unfavorable, however, due to severe interelectronic repulsion and a reduction in overlap attraction.<sup>19</sup>

Molecular Orbital Valence Bond (MOVB) theory is an attempt to rectify these shortcomings. What is of concern to us at present is what MOVB has to say with respect to delocalization in aromatic systems. If we digress momentarily and return to definitions of aromaticity what MOVB has to say will become apparent. In comparing the energies of benzene (BZ) and cyclohexatriene (CT) we make use of equation (4).

$$\Delta E_{\pi} = Q_{\pi} (CT) - Q_{\pi} (BZ) + \Delta J' \quad \text{Eq. (4)}$$

Normally it is assumed that  $\Delta J'$  is zero, where  $\Delta J'$  is the change in interelectronic repulsion energy. However, because BZ has available to it "ionic" CW's that are not present in a description of CT this assumption is invalid. This means that BZ has a set of charge transfer "ionic" CW's of the type shown in figure 1, that are unavailable to CT.



These ionic CW's are made unduly important because interelectronic repulsion is ignored. Since, according to MOVB,  $\Delta J'$  is in fact a significant factor,  $\Delta E_{\pi}$  is actually predicted to be of opposite sign than is traditionally thought. This is not to say that benzene is not a stabilized compound. It merely says that the stabilization benzene enjoys is not due to the pi system but rather in spite of it. That pi CT is more stable than pi BZ was implied by Eyring over 50 years ago by the Diatomics in Molecules method.<sup>20,21</sup>

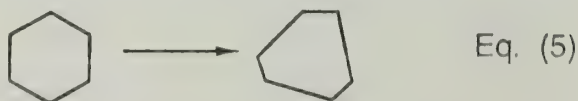
Thus if one were to consider two possible energy curves for pi bond exchange MOVB would predict Figure 2A to be operative while HMO would predict Figure 2B to be operating for the pi electrons of benzene.



Fig. 2

In order to look more closely at the validity of this model Shaik and Hiberty carried out computations on a variety of "resonance stabilized" systems and examined the effect of pi delocalization on the total energy of the system.<sup>21</sup>

The calculations were carried out using three different Gaussian contracted basis sets: STO-3G, 6-31G, and 6-311G. The main goal of the work was to separate effects due to the sigma framework from effects caused by the pi system. This was accomplished by three different methods. The first involved giving all pi electrons the same spin forming, in the case of benzene, the septuplet state. Calculations were then done on the sigma frame to measure the change in energy caused by a distortion of the type shown in equation (5).



The change in energy is then  $\Delta E_{dis}^{\sigma}$ . This value can then be used to obtain  $\Delta E_{dis}^{\pi}$  through use of equation 6.<sup>21b</sup>

$$\Delta E_{dis}^{\sigma,\pi} = \Delta E_{dis}^{\sigma} + \Delta E_{dis}^{\pi} \quad \text{Eq. (6)}$$

Another method by which the sigma frame is isolated is through calculations on the bare sigma framework in the absence of pi electrons making the hexacation. The value of  $\Delta E$  can again be obtained from Eq.7. The third method used to isolate the sigma and pi contributions to the distortion energy is the use of equation (7).

$$E_{tot}^{\sigma,\pi} = \sum h_{\pi}^{OCC} + R_{\pi\pi} + R_{\pi\sigma} + \sum h_{\sigma}^{OCC} + R_{\sigma\sigma} + V_{nn} \quad \text{Eq. (7)}$$

This equation allows partition of the distortion energy into sigma and pi components. The values of  $\Delta E^{TOT}$ ,  $\Delta E_{dis}^{\sigma}$ ,  $\Delta E_{dis}^{\pi}$  so obtained are collected in Table I.<sup>21</sup> It is readily apparent that the pi system of benzene is unstable toward distortion to localized double bonds. In concurrence with this observation similar calculations on cyclobutadiene and allyl radical yield a similar result.<sup>21</sup>

A general picture can be obtained by comparison of the above pi-systems with their isoelectronic  $H_n$ ,  $Cl_n$ , and  $Li_n$  analogues. It is found that atoms that form good overlap bonds, H for example, do not possess a strong propensity towards delocalization and have a distortion profile like 2A. Weak overlap binders, however, prefer delocalization and their profile is like 2B. Based upon bond energies and the calculations above, C pi systems must be placed in the class of atoms that prefer to be localized.<sup>21</sup> It is the sigma framework that holds the C atoms in place. Again it must be stressed that this result in no way denies the remarkable stability of benzene. Rather the results only place the credit for benzene's stability in other hands.

In conclusion, it would appear that pi delocalization is not the overwhelming driving force it is conventionally assumed to be. Rather, "aromatic" and "resonance" stabilization are a product of sigma effects.

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Table I

species	method	$\Delta E_{\text{dis}}^{\text{tot}}$	$\Delta E_{\text{dis}}^{\sigma}$	$\Delta E_{\text{dis}}^{\pi}$
STO - 3G				
C <sub>6</sub> H <sub>6</sub> (ground state)	SCF	+5.2	+17.1	-11.9
C <sub>6</sub> H <sub>6</sub> (ground state	$\pi$ - C I	+5.9	+17.1	-11.2
(C <sub>6</sub> H <sub>6</sub> ) <sup>+6</sup>	SCF		+17.3	
C <sub>6</sub> H <sub>6</sub> (septuplet)	SCF	+18.1	+16.9	
6 - 31G				
C <sub>6</sub> H <sub>6</sub> (ground state)	SCF	+6.6	+16.3	-9.7
C <sub>6</sub> H <sub>6</sub> (ground state	$\pi$ - C I	+7.2	+16.3	-9.1
(C <sub>6</sub> H <sub>6</sub> ) <sup>+6</sup>	SCF		+14.1	
C <sub>6</sub> H <sub>6</sub> (septuplet)	SCF	+14.5	+13.7	

# THE PREPARATION AND APPLICATIONS OF POLYMER-COATED SILICA GELS IN HIGH PRESSURE LIQUID CHROMATOGRAPHY

Reported by Kris Deming

October 26, 1987

Silica gel and its derivatives are utilized widely as stationary phases for many techniques in HPLC. Rigid synthetic organic polymers have also become very popular for separations in liquid chromatography. Both silica gel and organic polymers have advantages and disadvantages as stationary phases.<sup>1a,4e,15c,d</sup> Polymer-coated silica gel embodies some of the advantages of both types of stationary phase. Silica based polymer phases are derived by many different methods and applied to many types of HPLC.

Several different polymer-coated silica gel stationary phases have been prepared and utilized for ion exchange chromatography. Kimura described the synthesis and applications of some poly(crown ether)-modified silicas.<sup>1</sup> Igawa reported the separation of anions and cations on a silica-coated polyamide crown resin stationary phase.<sup>2</sup> Alpert developed a cation exchange stationary phase based on the reaction of poly(succinimide) with aminopropylsilica.<sup>3</sup> Regnier prepared both anion exchange and cation exchange stationary phases based on adsorption of polyethyleneimine onto silica gel.<sup>4,5</sup> Both Ueda<sup>6</sup> and Pfefferkorn<sup>7</sup> prepared cation and anion exchange stationary phases. Schomburg immobilized poly(2-hydroxy, 3-N-ethylenediamino) butadiene on the surface of silica to prepare a new anion exchange column.<sup>8</sup>

Alpert prepared a series of poly(alkyl aspartamide)-silicas for high-performance hydrophobic-interaction chromatography of proteins.<sup>9</sup> Regnier also prepared hydrophobic-interaction chromatography columns for the separation of proteins.<sup>10</sup>

Reversed-phase columns of a polymeric octadecyl silica gel were prepared for the separation of polynuclear aromatic hydrocarbons.<sup>11,12</sup> Silica gel adsorbed polyethyleneimine-based stationary phases were developed for the reversed-phase separations of biological macromolecules.<sup>13,14</sup> Schomburg immobilized polybutadienes or polysiloxanes on silica gel by various methods to produce reversed-phase columns.<sup>15</sup> A poly(vinylpyrrolidone)-coated silica was also prepared.<sup>16</sup>

Polyacrylamide treated with L-proline was adsorbed onto the surface of silica to produce a new ligand exchange column.<sup>17</sup> After Cu(II) was added as a complexing agent, enantiomeric resolution of  $\alpha$ -amino acids could be obtained. Another new ligand exchange column was prepared by bonding polymeric iminodiacetate to silica gel.<sup>18</sup>

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# CARBON-CARBON BOND FORMING REACTIONS OF ZIRCONOCENE COMPLEXES

Reported by Michael Wallace

October 29, 1987

## Introduction

Within the last decade, transition metal organometallic complexes have been used increasingly in organic transformations. The use of zirconocenes, bis(cyclopentadienyl) zirconium complexes ( $\text{Cp}_2\text{ZrX}_2$ ), as reagents to perform selective carbon-carbon bond formation has also increased dramatically. Two large areas of study in zirconocene chemistry are (1) the formation of zirconacyclopentanes from bis(olefin) zirconocene complexes (Figure 1); and (2) the addition of the Zr-H bond to an unsaturated organic substrate (hydrozirconation) and subsequent functionalization (Figure 2).



Figure 1. Formation of Zirconacyclopentane from bis(olefin) zirconocene complex.

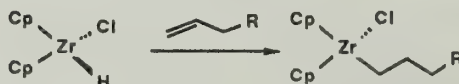
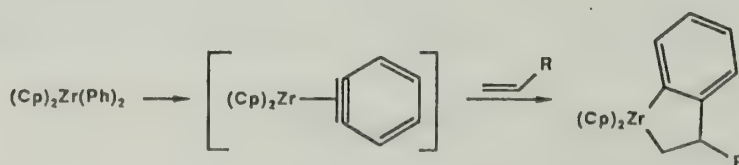


Figure 2. Hydrozirconation of an unsaturated organic substrate.

## Zirconacyclopentanes: Mechanism Of Formation

Although several bis-olefin  $d^0$ -metallacene complexes had been studied before,<sup>1</sup> Gerhart Erker was the first to propose an intermediate aryne-zirconocene complex in 1977.<sup>2</sup> Erker realized the replacement of an olefin with a high energy aryne would favor formation of the metallacycle from the bis(olefin) zirconocene complexes. Pursuit of this idea led to the synthesis and study of zirconaindans.<sup>3</sup>

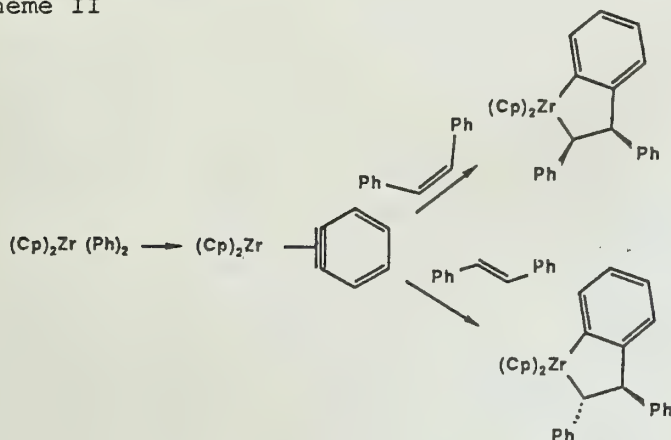
### Scheme I





Erker examined the stereospecificity of zirconaindan formation as a criterion for concertedness of ring closure.<sup>4</sup> Erker's observation of 99% selectivity based on the starting olefin stereochemistry provides strong evidence for a concerted ring closure of olefin-aryne complex to metallacycle (Scheme II).

Scheme II



Buchwald has been able to trap, isolate, and characterize Erker's proposed high energy aryne intermediate as the trimethylphosphine adduct (1).<sup>5</sup> The crystal structure of each complex (1-4) reveal that they resemble a metallacyclopropene rather than a aryne-metal complex, an indication of severe backbonding to the  $d^0$  metal center. Buchwald has synthesized the trimethylphosphine zirconocene-stabilized complex of benzidyne (2),<sup>6</sup> cyclohexyne (3),<sup>7</sup> terminal and internal alkynes (4)<sup>8</sup> (Figure 3). The mechanism of formation, proposed by Erker,<sup>2</sup> involves CH bond activation with simultaneous loss of methane (Scheme III).

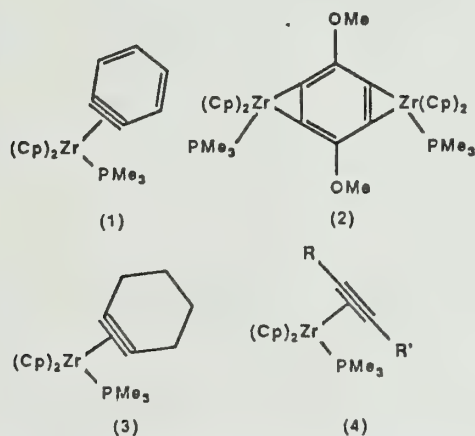
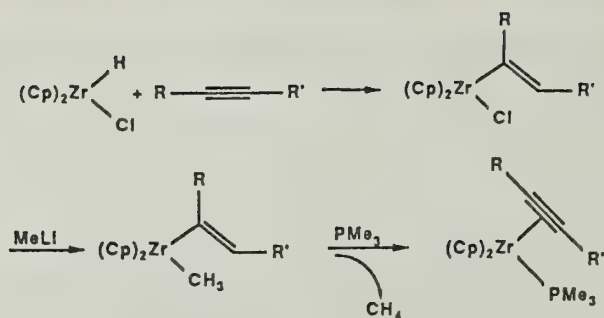


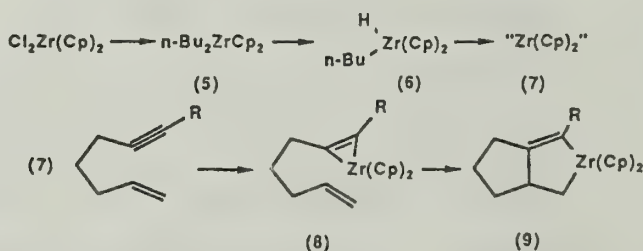
Figure 3. Buchwald's Zirconocene Trimethylphosphine stabilized "Eyne" Complexes

Scheme III



Negishi has examined the cyclizations of enynes <sup>9,10,11</sup>, dienes,<sup>11</sup> and diynes<sup>11</sup> using the " $\text{Zr}(\text{Cp})_2$ " reagent prepared from treatment of  $\text{Cl}_2\text{ZrCp}_2$  with two equivalents of  $n\text{-BuLi}$ . Mechanistic studies<sup>11</sup> indicate an initial formation of a dibutyl species (5), followed by an elimination of 1-butene. The monobutyl species (6) undergoes a reductive elimination to yield the intermediate zirconocene (7) which then reacts with dienes or diynes by oxidative coupling to produce a species similar to Buchwald's stabilized complexes. The metallacyclopentene (8) then complexes another unsaturated ligand and forms the metallacycle (9) (Scheme IV).

Scheme IV.



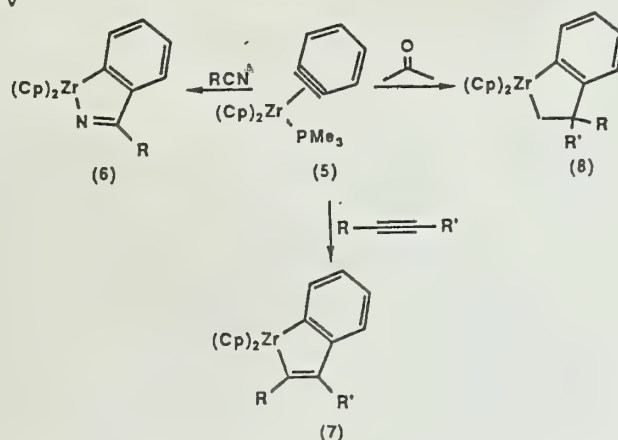
Nugent has examined the intramolecular cyclization of diacetylenes to yield E,E exocyclic dienes.<sup>12</sup> Mechanistic studies indicate an initial  $n^2$  acetylene complex, and crystal structures have provided insight into the mechanism of carbocycle formation. Since the carbocyclic ligands and metal are coplanar, coordination and cyclization is postulated to occur in a single plane. To further understand the facility of cyclizations and bonding involved, Nugent carried out molecular orbital calculations on (acetylene) bis(cyclopentadienyl) zirconium (II). Optimization indicated the acetylene preferred to be parallel to the Cp ligands and bent at a  $20^\circ$  angle. It is this movement of the acetylene which exposes a HOMO (pi donor) and LUMO (sigma acceptor) which is capable of binding the second

acetylene. Once the acetylene is in the coordination sphere, the coupling process is symmetry allowed as according to Woodward and Hoffmann.<sup>13</sup>

### Synthetic uses of Zirconacyclopentanes and Related Compounds

Zirconacycles can be exploited to perform several interesting synthetic transformations. Buchwald's isolable zirconocene-benzynes (5) reacts with nitriles, alkynes, and ketones to form azametallacycles (6), metallacyclopentadienes (7), and metallaoxiranes (8) respectively<sup>5</sup> (Scheme V). These metallacyclopentadienes may be carbonylated, hydrolyzed, or cleaved with halogen according to the methods established by Negishi.<sup>9</sup>

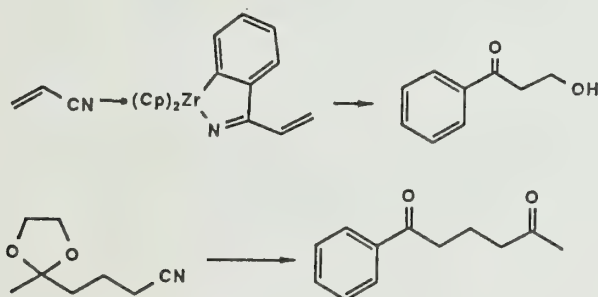
Scheme V



Benzidyne reacts similarly with nitriles, alkynes, and ketones to produce the corresponding zirconacycles.<sup>6</sup> Protonolysis of the benzidyne complex shows that it can be used as an aromatic tetraanion equivalent. Zirconocene complexes of both cyclic and acyclic alkynes show the same reactivity toward nitriles, ketones, and alkynes<sup>7,8</sup> and allowing hydrolysis yield the corresponding products.

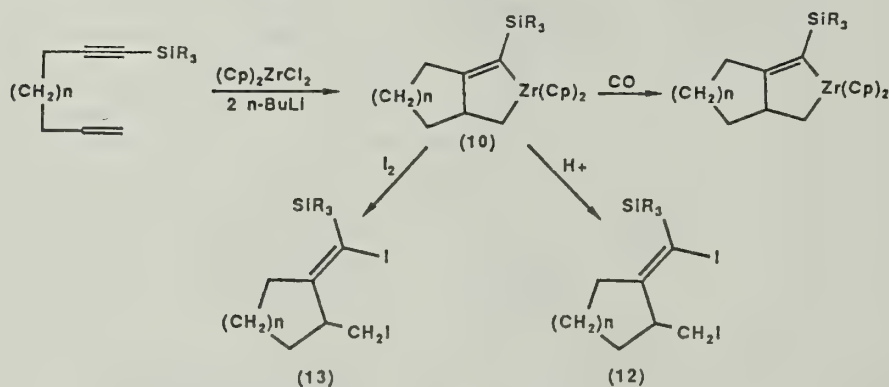
Hydrolysis of azametallacyclopentanes leads to ketones, thus the overall transformation is equivalent to a Friedel-Crafts acylation.<sup>15</sup> The advantage of this method is that it tolerates substrates with acid sensitive functional group (Scheme VI).

Scheme VI.



Negishi has studied the cyclizations of enynes<sup>9,10,11</sup>, dienes<sup>11</sup>, and diyne<sup>11</sup> using the "Zirconocene" reagent to produce zirconabicyclic derivatives. The isolable intermediate (10) may be carbonylated, hydrolyzed, or cleaved with iodine to yield the  $\alpha$ -B unsaturated bicycle (11), exocyclic alkene (12), or diiodo species (13) respectively (Scheme VII). The trimethylsilyl group was difficult to replace so Negishi developed the bicyclic closure using trimethyltin which allowed for functionalization at the  $\alpha$  position while retaining the bicyclic structure.

Scheme VII



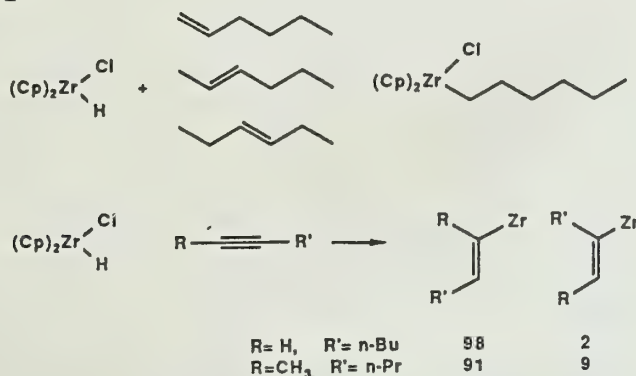
### Hydrozirconation; Carbon-Halogen and Carbon-Carbon Bond Formation

Addition of the Zr-H bond to unsaturated organic substrates (hydrozirconation) and subsequent functionalization of the organozirconocene complexes has been studied for over 15 years.<sup>16</sup> In most cases of attachment of the zirconocene to the unsaturated substrate occurs at the least sterically hindered position. This proceeds through either regiospecific attachment to the terminal olefin or a rapid rearrangement through Zr-H elimination.<sup>17</sup> Recently, however, Gibson has observed that aromatic olefins give mixtures of benzylic and terminally substituted alkyl zirconium complexes.<sup>18</sup> By examining the oxidation of these secondary centers, Gibson was able to show that oxidation occurs with retention of



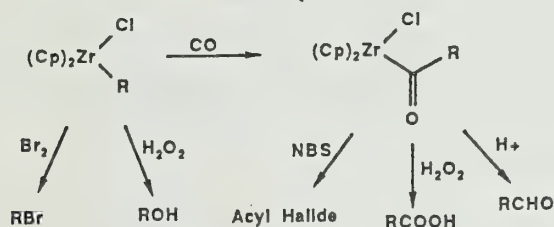
stereochemistry. Addition to terminal alkynes also proceeds stereospecifically and regiospecifically to yield the cis-isomer with Zr unit on the end. Disubstituted alkynes yield regioisomeric mixtures in which steric bulk determines the attachment of the zirconocene (Scheme VIII).<sup>19</sup>

Scheme VIII



Functionalization of organozirconium complexes provides access to a wide range of functional groups. Halogenolysis, with electrophilic reagents such as bromine, iodine, or N-Bromosuccinimide yield the corresponding halides.<sup>17,19</sup> Zirconium-carbon bonds may also be oxidized with hydrogen peroxide to yield alcohols<sup>20</sup>. Carbon monoxide cleanly inserts into zirconium-carbon bonds to generate acylzirconium complexes which may be subsequently converted into aldehydes, esters and acids<sup>21</sup> (Scheme IX). Buchwald has recently<sup>22</sup> devised a mild procedure using hydrozirconation for anti-Markovnikov hydrocyanation of olefins and acetylenes which tolerates a variety of functional groups.

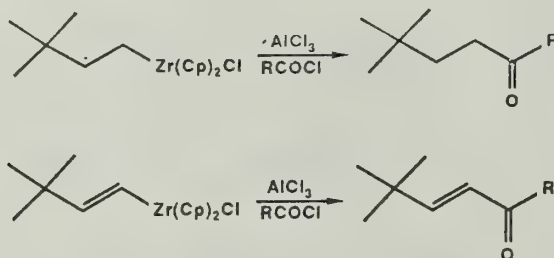
Scheme IX



Except for homologation via CO insertion, hydrozirconation of olefins and acetylenes has not been effective for direct C-C bond formation.

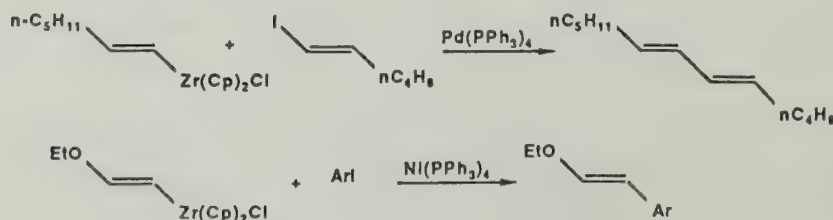
Acylation can only be accomplished only if steric factors are held to a minimum.<sup>23</sup> As a result, several methods of transmetalation, either stoichiometrically or catalytically, have been developed to produce reactive intermediates capable of carbon-carbon bond formation. Stereospecific transmetalation of alkylzirconium complexes can be accomplished by treatment with AlCl<sub>3</sub> to yield the organoaluminum dichlorides <sup>23,24</sup> which can then be acylated to yield the corresponding ketones (Scheme X).

Scheme X



Negishi has developed one of the most versatile and widely used pathways to trisubstituted olefins by the treatment of acetylenes with  $\text{Me}_3\text{Al}-\text{Cl}_2\text{ZrCp}_2$  yielding E-2-methyl-1-alkenylalanes.<sup>25</sup> Catalytic in Zr, carboalumination, yields exclusively cis alkenylalanes and can tolerate several other functionalities in the acetylene such as Cl, OH, and SPh, without loss of regioselectivity.<sup>26</sup> These alkenylalanes can further react with n-BuLi to yield the "ate" complex which then react stereospecifically with epoxides, alkyl halides, and aldehydes.<sup>27</sup> The alkenylalanes can also couple through Ni or Pd catalysis, with aryl or alkenyl halides.<sup>28</sup> In addition, Negishi has shown that alkenylzirconium derivatives can couple directly with aryl,<sup>29</sup> alkenyl,<sup>29</sup> allylic<sup>30</sup>, and alkynyl<sup>29</sup> halides in the presence of Ni or Pd phosphine complexes (Scheme XI) via an oxidative addition, transmetalation, reductive elimination pathway

Scheme XI



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## CHIRAL PHASE TRANSFER CATALYSIS

Reported by John McCune

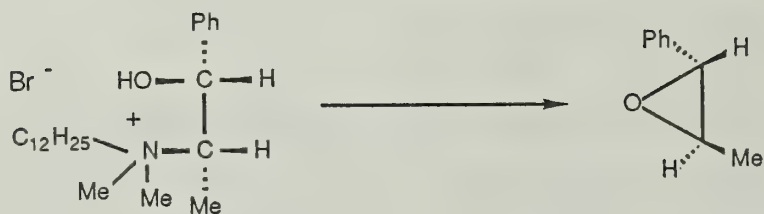
November 9, 1987

Efficient asymmetric synthesis is a topic of significant importance in organic chemistry. One route to potentially simple asymmetric induction is chiral phase transfer catalysis. Phase transfer catalysis methods offer several advantages: expensive anhydrous or aprotic solvents are not required, improved reaction rates can be achieved and lower reaction temperatures may be utilized. In addition increased yields through suppression of side reactions, and in many cases an easier workup may be realized. These characteristics, coupled with the obvious attractiveness of asymmetric synthesis, suggest the importance of developing chiral phase transfer catalysis methods.

The first reaction utilizing a chiral phase transfer catalyst (chiral PTC) was reported in 1975.<sup>1</sup> There are currently five types of chiral PTC's: (1) quaternary ammonium salts, (2) crown ethers,<sup>2</sup> (3) polyamino-acids<sup>3</sup> and proteins,<sup>4</sup> (4) polymers, and (5) metal complexes.<sup>5</sup> Quaternary ammonium salts and polymers have been by far the most widely studied. Polymer based chiral PTC's have been reviewed.<sup>6</sup> This paper will concentrate on the quaternary ammonium salt chiral PTC's.

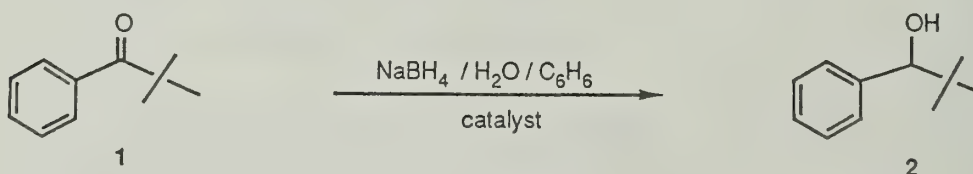
Numerous reports of asymmetric induction by chiral PTC's proved to be inaccurate upon close examination.<sup>1,7</sup> The optical purity in each of these cases was determined by observed optical rotations of the product, O.P. =  $[\alpha]_{\text{obs}}^{25} / [\alpha]_{\text{max}}^{25} \times 100$ . There are two possible sources of error in such experiments<sup>8</sup>: (1) Quaternary amines used as chiral PTC's decompose readily under the reaction conditions to give an optically active oxirane of very high specific rotation, Scheme 1. (2) The process of quaternization is almost invariably accompanied by the formation of small amounts of tertiary amine hydrohalide. Workup of the reaction and removal of the PTC regenerates the optically active free amine. Impurities from either process or compounds derived from these impurities may lead to false claims of asymmetric induction. Products must be purified meticulously to avoid errors and extreme care must be exercised in the evaluation of experimental results. Consequently literature claims must be viewed critically. The determination of optical purity by NMR, via chiral shift reagents, or HPLC assay on a suitable chiral stationary phase is desirable. These methods are unaffected by the problems inherent in determinations by optical rotations.

Scheme 1



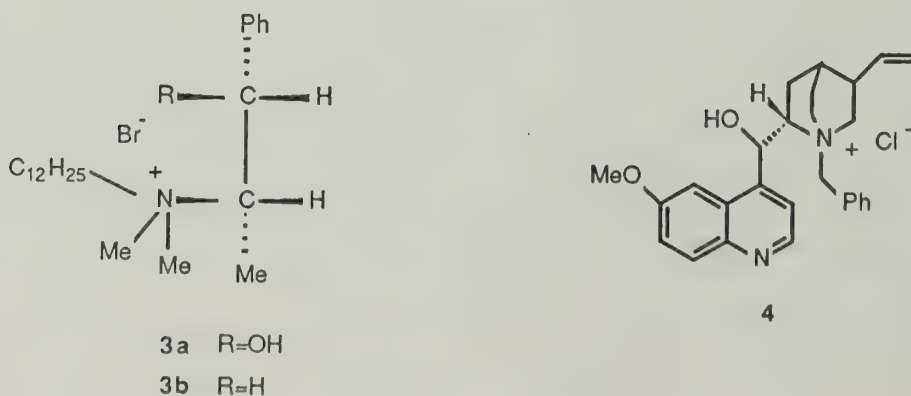
Investigations into asymmetric induction in the borohydride reduction of carbonyl compounds by means of a chiral PTC have been reported.<sup>2b,9</sup> Optical purities have been modest, a maximum of 32% ee being the highest reported. Asymmetric reduction of phenyl-*tert*-butyl ketone, **1**, to phenyl-*tert*-butylcarbinol, **2**, with NaBH<sub>4</sub> under phase transfer conditions was attempted with three different chiral PTC's; (-)-N-dodecyl-N-methylephedrinium bromide, **3a**, (-)-(R)-N,N-dimethyl-N-dodecylamphetaminium bromide, **3b**, and benzylquininium chloride **4**.<sup>10</sup> The results are summarized in Table 1.

Table 1



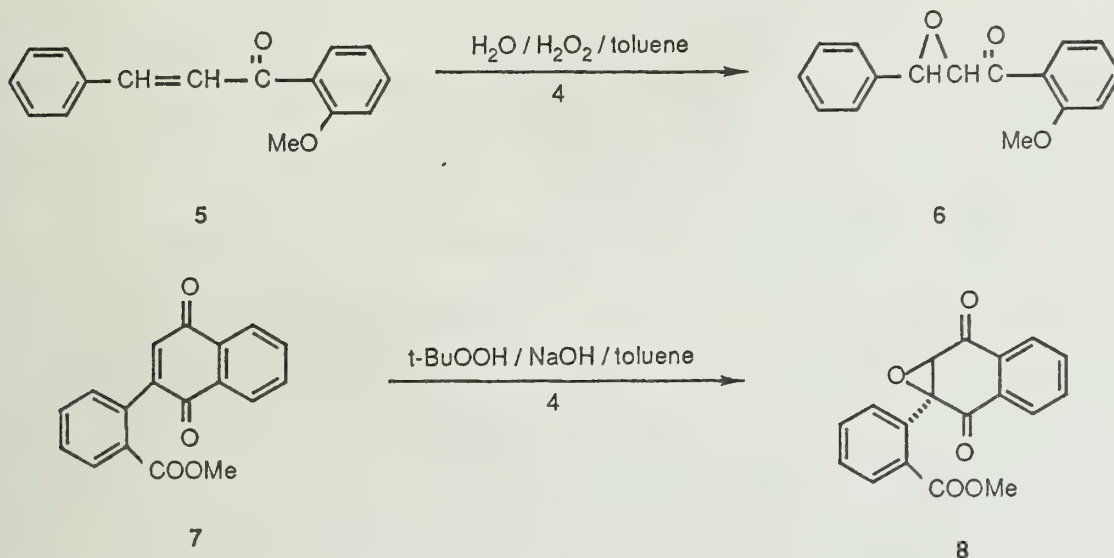
Catalyst	Reaction Conditions	Yield (%)	Optical Purity (%)†
3a	0°/1h	77	4.2
3b	0°/1h	61	0.0
4	0°/1h	95	32.0

† determined by optical rotations, o.p. =  $[\alpha]_{\text{obs}}^{25} / [\alpha]_{\text{max}}^{25} \times 100$



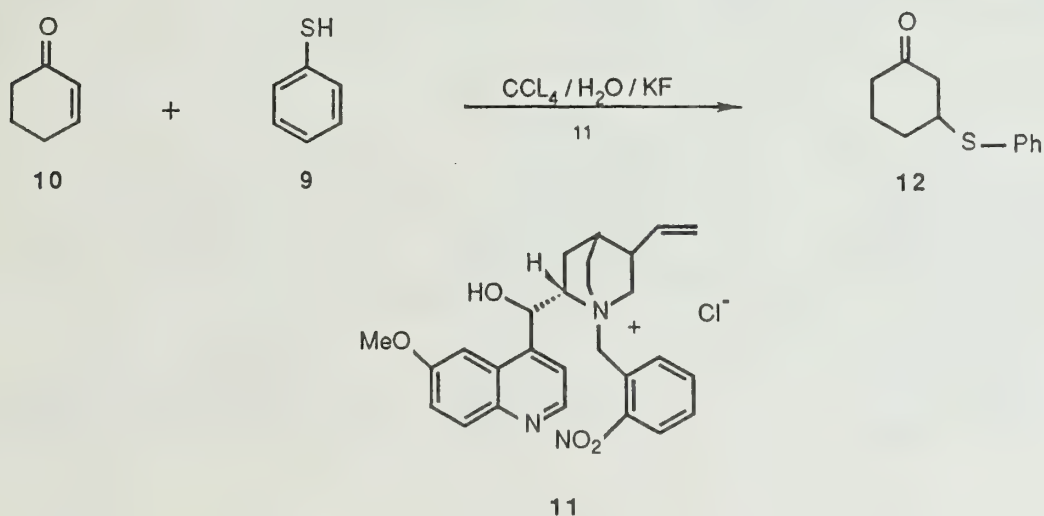
Structural requirements for the chiral PTC can be inferred from the data. The presence of a hydroxy-group in the catalyst is essential to achieve asymmetric induction and a conformationally rigid, e.g. **4**, chiral PTC is desirable.

Chiral PTC's have been used in the synthesis of optically active epoxides.<sup>11</sup> The optical purity was modest at best. Wynberg and co-workers reported a 99% yield with a 25% ee (determined by NMR) when chalcone **5** was epoxidized with **4** as the chiral PTC to give **6**.<sup>10e</sup> An asymmetric epoxidation of quinone **7** with *t*-butyl hydroperoxide and **4** as the chiral PTC gave **8** in 95% yield and 78% ee (determined by NMR).<sup>12</sup>

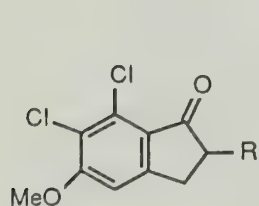


Addition of chlorine to alkenes and asymmetric nucleophilic substitutions with carbon, nitrogen, oxygen and sulfur anions under phase transfer conditions with a chiral catalyst have been reported.<sup>13</sup> Asymmetric induction in the Michael reaction by means of a chiral PTC has been investigated.<sup>14</sup> Addition of thiophenol, **9**, to cyclohexene, **10**, with *N*-(*o*-nitrobenzyl)quininium chloride, **11** as chiral PTC gives **12** in 85% yield with a 36% ee (determined by optical rotation), Scheme 2.

Scheme 2

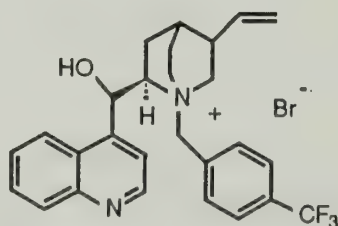


An efficient enantioselective methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone, **13a**, using N-(p-(trifluoromethyl)benzyl) cinchoninium bromide, **14**, as chiral PTC was reported.<sup>15</sup> Product **15a** was obtained in up to 95% yield with a 92% ee. The enolate of **13a** has the negative charge delocalized into the 2-phenyl ring and has an almost planar conformation. X-ray analysis and molecular modeling studies of the benzylcinchoninium ion indicated that a conformation in which the quinoline ring, the N-benzyl group and the C<sub>9</sub>-O bond all lie in a plane is preferred, the quinuclidine ring lies behind the plane. The planar conformations of the two molecules allow them to stack together nicely. Hydrogen bonding of the C<sub>9</sub>-hydroxyl proton to the indanone anion and  $\pi$  acid- $\pi$  base interactions between the quinoline and 3-methoxydichlorobenzene moieties, and the 2-phenyl group of **13a** and the benzyl group of **14** provide three points of interaction between the catalyst and substrate (Figure 1). The catalyst effectively blocks the backside of **13a**, allowing alkylation only from the front side to give the (S)-(+)-2-methylindanone, **15a**. If ion pairing as depicted in Figure 1 is important, then asymmetric induction should be sensitive to the electronic effects of substituents on the N-benzyl group. Substituents (CH<sub>3</sub>, CH<sub>3</sub>, F, Cl) other than CF<sub>3</sub> on the N-benzyl group give ee's of 60-80%. A Hammett plot of  $\log (ee/ee_0)$  vs.  $\sigma$ , the substituent constant of the para-N-benzyl substituted catalysts, gave a reaction constant of  $\rho = 0.21 \pm 0.02$ , thus demonstrating that catalyst selectivity is improved with increasing electron-withdrawing power of the substituent and supporting the ion pairing scheme. The degree of asymmetric induction was dependent on the reaction conditions. Nonpolar solvents, toluene or benzene, gave higher ee's than polar solvents, methylene chloride or methyl *t*-butyl ether. The catalyst concentration had little effect on asymmetric induction but was the controlling factor in the rate of reaction. Decreasing the concentration (14 to 7 mol/mol of **13a** at 15 °C) of the alkylating agent improved the ee from 84% to 96% (40% yield). Temperature affected both the rate and ee. Lowering the temperature from 25 to 5 °C, with all other variables constant, increased the ee to 90% from 78%, but slowed the rate of reaction substantially. The choice of alkylating agent also affected selectivity, CH<sub>3</sub>Cl being superior to both CH<sub>3</sub>Br and CH<sub>3</sub>I. Excellent agitation was crucial.

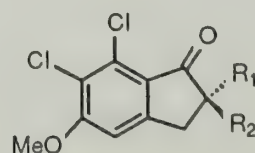


**13a** R=C<sub>6</sub>H<sub>5</sub>

**13b** R=n-C<sub>3</sub>H<sub>7</sub>



**14**



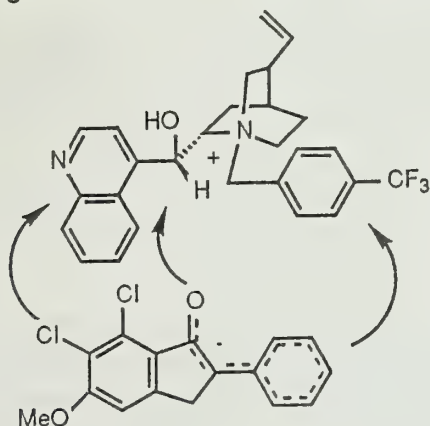
**15a** R<sup>1</sup>=C<sub>6</sub>H<sub>5</sub> R<sup>2</sup>=CH<sub>3</sub>

**15b** R<sup>1</sup>=n-C<sub>3</sub>H<sub>7</sub> R<sup>2</sup>=-CH<sub>2</sub>CH=C(Cl)CH<sub>3</sub>



Alkylation of 6,7-dichloro-5-methoxy-2-propyl-1-indanone, **13b**, with 1,3-dichloro-2-butene in analogy to the procedure described for **13a** with **14** as chiral PTC produced (S)-(+)-6,7-dichloro-2-(3-chloro-2-butenyl)-5-methoxy-2-propyl-1-indanone, **15b** in 92% ee (determined by NMR) and 99% yield.<sup>16</sup> The tight ion pair proposed for the alkylation of **13b** is analogous to that proposed in Figure 1, except the  $\pi$ - $\pi$  interaction between the 2-phenyl group of **13a** and the benzyl group of the catalyst is replaced by an attractive nonbonded alkyl- $\pi$  interaction between the 2-propyl group of **13b** and the benzyl group of **14**. The remaining  $\pi$ - $\pi$  interaction and hydrogen bond proposed in Figure 1 prevails. A Hammet plot of  $\log(ee/ee_0)$  vs.  $\sigma$  for para-N-benzyl substituted catalysts gave a  $\rho$  value of 0.67 for **13b** as opposed to  $\rho = 0.21$  for **13a**. The delocalization of the negative charge of the enolate anion into the phenyl ring in **13a** is absent in **13b**. Accordingly, **13b** responds toward substituent effects in the catalyst to a greater extent. These two examples of truly efficient enantioselective alkylations mediated by chiral PTC's offer potential in terms of simplicity, ease of operation, and enantio-specificity.

Figure 1

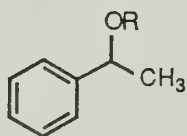


The mechanistic pathway of chiral PTC reactions has not been well addressed. Stereoselectivity seems to be affected by solvent polarity, structure of the substrate, reaction conditions<sup>9a,10a,11a,17</sup> and structure of the chiral PTC. There are two types of ion pairs; loose, external or solvent separated ion pairs and tight, internal, intimate or contact ion pairs. The latter being necessary for high asymmetric induction. The choice of solvent strongly affects the formation of ion pairs. Polar protic solvents solvate both anions and cations and lead to a high degree of dissociation into free solvated ions. Polar aprotic solvents readily solvate cations and also prevent tight ion pairing. Phase transfer catalysis reactions are usually carried out in aprotic solvents of low polarity. The use of more polar solvents leads to reduced enantioselectivity. The reaction parameters also strongly affect the degree of asymmetric induction. Lower temperatures afford higher ee's. Salting-out effects are observed. For example, with 50% aq. NaOH almost all quaternary ammonium salts are sparingly soluble and

easily extracted into the organic phase. Addition of an inorganic salt as co-catalyst also acts as an organic phase dessicant. The action of salt is then two-fold: it separates the organic solvent and salts out the ion pairs.

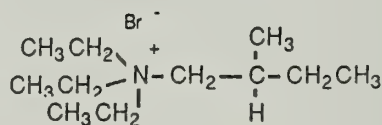
Typically a quaternary ammonium salt which possesses a A-hydroxy group serves as the chiral PTC. The highest asymmetric inductions have been obtained with conformationally rigid chiral PTC's. The catalyst should have at least three potential points of interaction with the substrate and effectively block all but one approach to the substrate. If these conditions are not met the degree of asymmetric induction will be reduced because alternative avenues of approach will be available to the reactant.

All rules have exceptions, an alkylation reaction with a nonfunctionalized optically active PTC has been described.<sup>18</sup> Methylation of racemic **16a** with **17** as chiral PTC gave (R)-(+)-1-phenyl-1-methoxyethane, **16b**, in 48% ee (determined by optical rotation) and 75% yield. The claimed enantiomeric excess could not be verified by NMR and resolution by HPLC on a chiral stationary phase was not attempted.



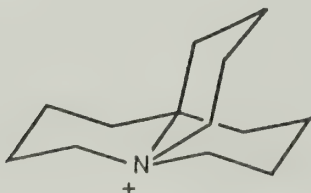
**16a** R=H

**16b** R=Me

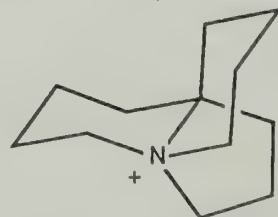


**17**

Chirality of the catalyst is usually obtained in the carbon skeleton of the salt, **3a** or in both the carbon skeleton and the nitrogen atom of the salt, **4**. No examples of the successful use of a chiral PTC where the chirality is due solely to the nitrogen atom have been reported. McIntosh has synthesized and identified compounds **18** and **19**.<sup>19</sup> The preparation of substituted systems and evaluation of their utility as PTC's is in process. Compounds such as **18** and **19** are ideally suited to study the mechanistic requirements of chiral PTC. They possess a chiral nitrogen atom with three faces of the nitrogen atom blocked, are conformationally rigid and introduction of substituents in stereochemically defined ways is possible.



**18**



**19**

In conclusion, highly enantioselective reactions have been performed with a chiral catalyst under phase transfer conditions. In consideration of the advantages over conventional methods and the high ee's which can be obtained, chiral PTC development and elucidation of the mechanistic pathway is of considerable interest to organic chemists.

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# CHIRAL NAD(P)H MODELS AS PROBES FOR THE STEREOSELECTIVITY OF DEHYDROGENASES

Reported by Carol Lamberson

December 3, 1987

## Introduction

Enzymes can catalyze reactions with high regio- and stereoselectivity due to the asymmetric environment of the enzyme active site.<sup>1</sup> To examine the factors that control enzyme stereospecificity, chemists have attempted to mimic enzymes by preparing small molecules containing the important functional groups of the active site. In particular, the nicotinamide adenine dinucleotide, NAD(P)H, (Figure 1) dependent enzymes have been studied quite extensively in recent years.<sup>2</sup> Studies have concentrated on modeling the stereospecific reduction of carbonyl compounds by alcohol and lactate dehydrogenases. These NAD(P)H model systems contain at least one stereogenic center and a few can reduce activated carbonyl compounds with 90 to 99 % enantiomeric excess (ee). Refinement of these models may produce useful reagents for asymmetric synthesis.

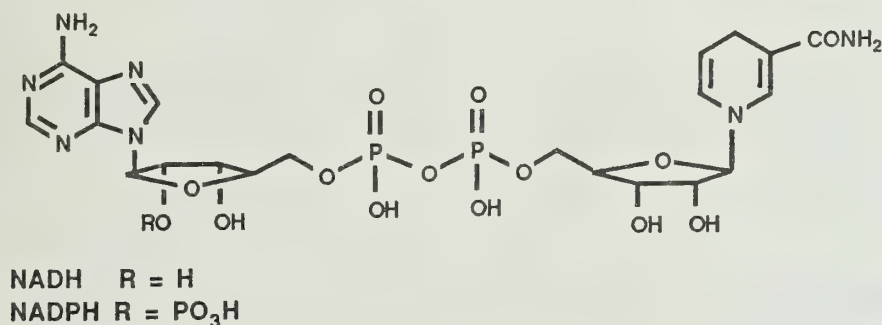


Figure 1. Structure of the Nicotinamide Adenine Dinucleotides.

## The Enzyme Reaction

In general, the dehydrogenases reversibly catalyze the redox reaction:



Despite the variability of the dehydrogenases active sites,<sup>1</sup> they all contain a functional group which activates the substrate for reaction. In the alcohol dehydrogenases, a zinc atom is located in the active site,<sup>3</sup> whereas all other dehydrogenases contain an imidazole of a histidine residue.<sup>4</sup> The imidazole

group and the zinc atom have been proposed to activate the substrate by complexation to its carbonyl or alcohol oxygen atom.<sup>1</sup>

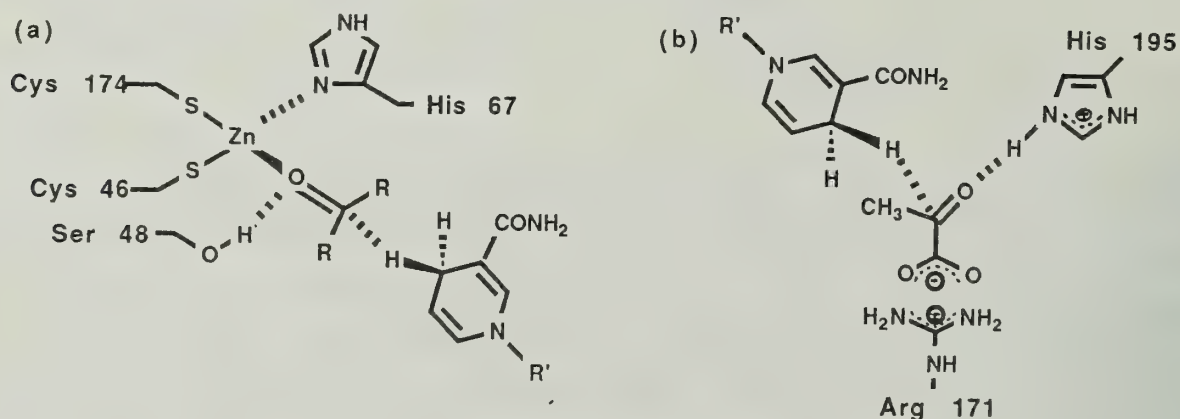
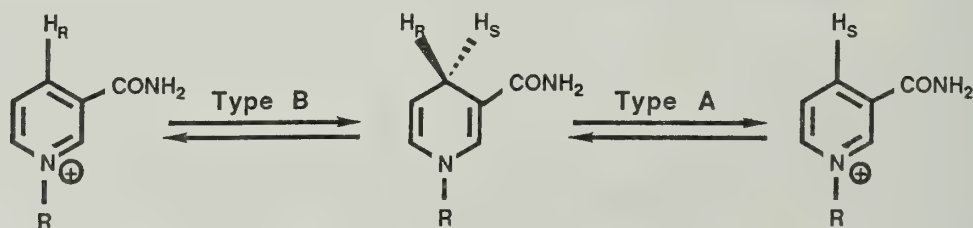


Figure 2. Proposed ternary structures for (a) Horse liver alcohol dehydrogenase and (b) L-lactate dehydrogenase.

With respect to the stereospecificity of the dehydrogenases, it is known that some enzymes selectively transfer the pro-R hydrogen while others transfer the pro-S hydrogen<sup>1</sup> (Scheme I).

Scheme I



### The Mechanism for Reduction

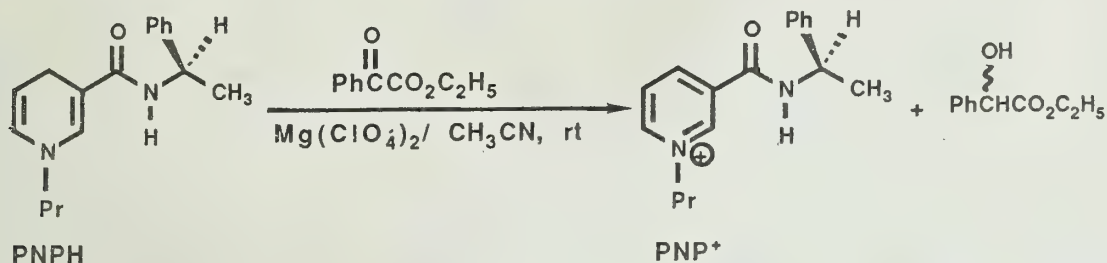
The mechanism in both the enzymatic and non-enzymatic systems is controversial. The main concern is whether the reaction proceeds by a direct hydride transfer<sup>5</sup> or a multistep process in which a single electron transfer is the initial step.<sup>6</sup> However, the majority of theoretical<sup>7</sup> and experimental evidence supports the direct hydride transfer mechanism for both enzymatic and model systems.

### Chiral NAD(P)H Models

The first successful asymmetric reduction with a chiral NAD(P)H model was achieved by Ohnishi and coworkers<sup>8</sup> (Scheme II) in which a dihydropyridine derivative containing a remote chiral center quantitatively reduced ethyl

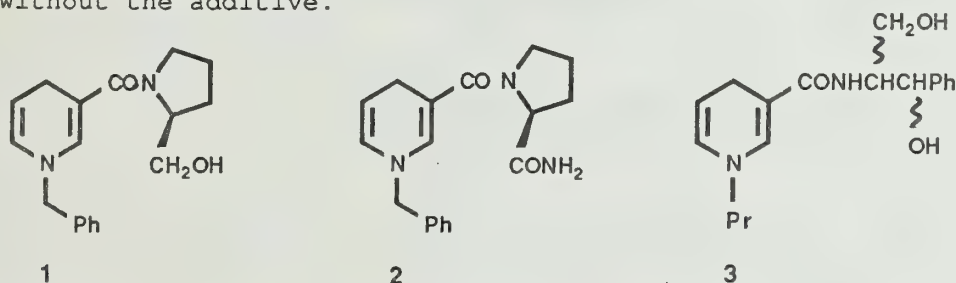
benzoylformate to ethyl mandelate with a 20 % ee of the R enantiomer. Further studies on this model compound with various activated ketones led to the conclusion that the magnesium ion plays a crucial role in acceleration of the reaction as well as contributing to the asymmetric induction.<sup>9</sup> Additional work indicated that the magnesium ion is actually complexed to the pi-orbital of the dihydropyridine ring;<sup>10</sup> thus, it was suggested that a ternary complex is formed between the model compound, the metal ion, and the substrate.

Scheme II



Another phenomenon initially noticed by Ohnishi<sup>11</sup> in the reduction of ethyl benzoylformate with PNPH was that the asymmetric induction of the carbinol product was dependent on the percent conversion of the reactants. Specifically, the ethyl mandelate isolated after a short reaction time had a configuration opposite the carbinol product isolated when the reaction had gone to completion.

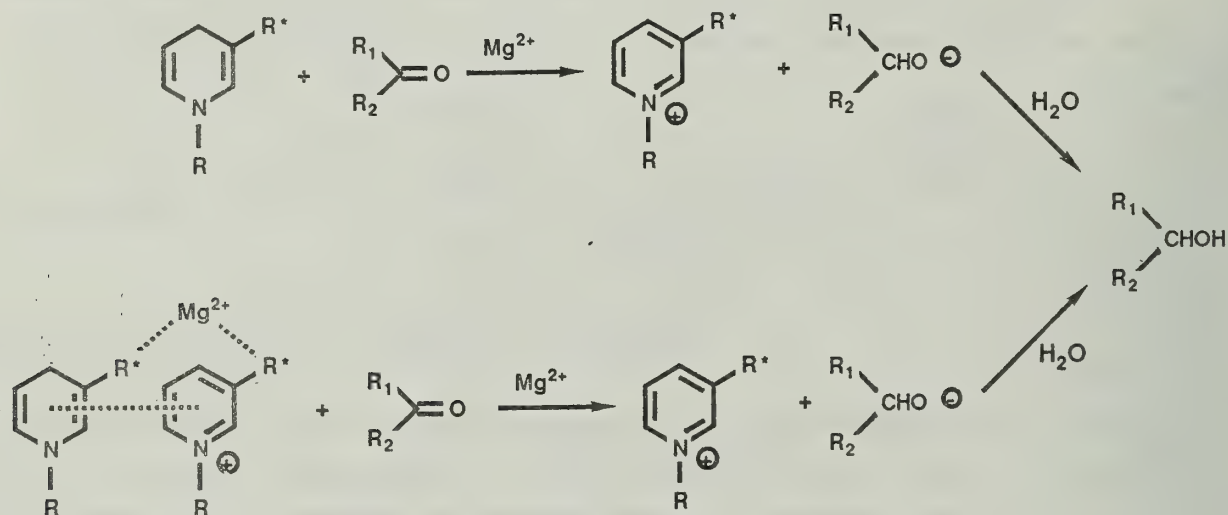
Similar results were obtained by Inouye and coworkers<sup>12</sup> in the reduction of ethyl benzoylformate with models 1 and 2. They did not observe a change in configuration of the product, but they did find that the optical yield was a function of the extent of the reaction. Additionally, Inouye et. al.<sup>13</sup> examined the effect of pyridine and pyridinium salts on the reduction of ethyl benzoylformate with compound 3. It was found that the additive caused a dramatic increase in the final optical yield of the product relative to the reduction without the additive.



They proposed a feedback type mechanism<sup>12b</sup> in which the oxidized form of the model, which is a good electron acceptor, interacts with the reduced form

of the model through chelation mediated by the magnesium ion and possibly by a charge transfer attraction. This interaction causes specific blockage of one face of the dihydropyridine ring which contributes to the improvement of the optical yield at later stages of the reaction (Scheme III).

Scheme III



To support the possibility of a dihydropyridine-magnesium ion chelation complex, a chiral polymethylene-bridged Bis(NADH) model was examined.<sup>14</sup> Using UV spectroscopy, these compounds were found to form 1:1 chelation complexes with magnesium, and the  $n=6$  compound reduced ethyl benzoylformate with a 95.6 % ee. The results indicated that the two dihydropyridine rings were complexed through a magnesium which forces reduction to occur from the less hindered face of the dihydropyridine ring (Figure 3).

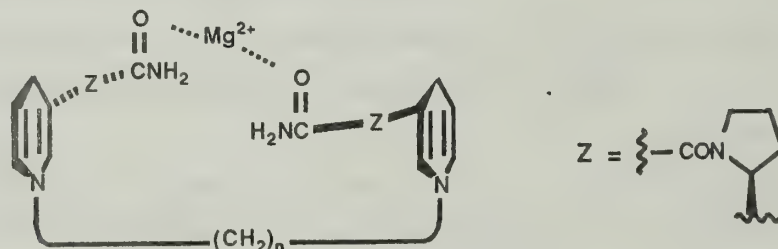


Figure 3. Possible Bis(NADH) reaction species.

To examine the factors which influence the orientation of the substrate relative to the dihydropyridine ring in the transition state, Ohno et. al.<sup>15</sup> prepared a model in which one of the C-4 hydrogens was replaced with a methyl group (Scheme IV, Table 1). Since there is only one hydrogen available for



reduction, reaction can only occur from one face of the dihydropyridine ring. Thus, the configuration of the carbinol product reflects the orientation of the substrate in the transition state. Ohno examined the effect of the ketone substituents on the asymmetric reduction with the 4R9R, 4S9R, and 4S9S derivatives of Me<sub>2</sub>PNPH.<sup>15,16</sup> The authors noticed that the stereochemistry of the reduction was not significantly effected by the size of R and R' but was dependent on the polarity of the substituents. Ohno concluded that the more

Scheme IV

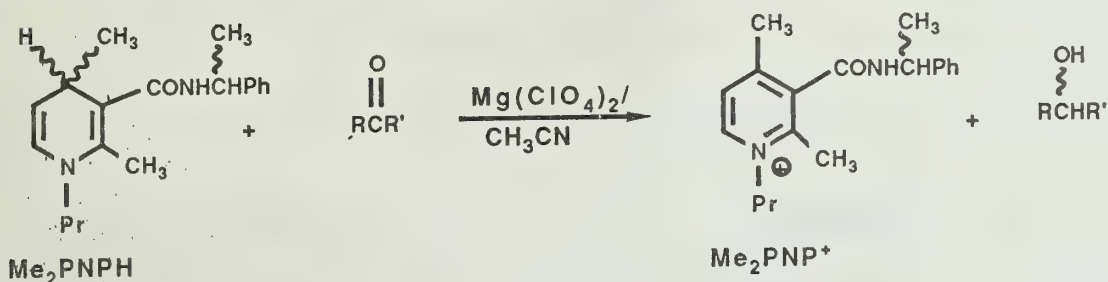


Table 1. Reduction of activated ketones with Me<sub>2</sub>PNPH.

R	R'	configuration of Me <sub>2</sub> PNPH	conversion (%)	product configuration	optical yield, (%)
Ph	CO <sub>2</sub> CH <sub>3</sub>	RR	100	R	97.6
"	"	SR	100	S	96.5
t-butyl	CO <sub>2</sub> CH <sub>3</sub>	RR	95	R	99.0
m-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> -	CF <sub>3</sub>	SS	100	R	99.0
2-pyridyl	CH <sub>3</sub>	RR	100	R	62.8

polar substituent on the ketone must be located on the same side as the amide group on the dihydropyridine derivative (Figure 4).

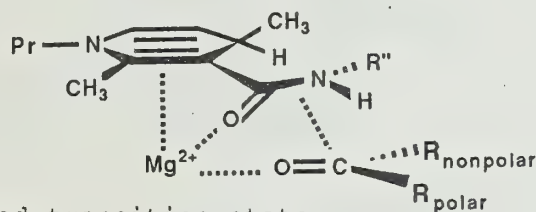


Figure 4. Ohno's proposed transition state.

The orientation of the carbonyl group relative to the dihydropyridine nitrogen atom, as well as the trajectory for the hydride transfer are points

which have been addressed by other workers. It was proposed by Prelog<sup>17</sup> that the reacting carbonyl oxygen points toward the ring nitrogen atom to diminish non-bonding interactions and to achieve maximum orbital overlap. However, MNDO calculations with full geometry optimization on the possible transition states indicate that the transition state is linear and that the parallel-exo and tilted-endo geometries can be interconverted by rotation of the rings relative to each other around the C4-H-C axis<sup>7,18</sup> (Figure 5).

In Ohno's model, the hydride can only be transferred from one face. If his polarity argument is sound, the configuration of the major product

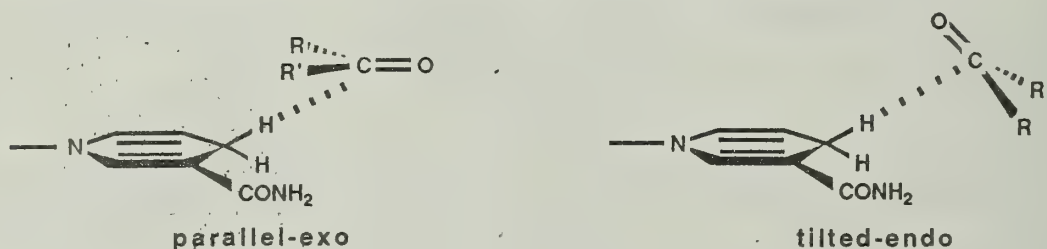


Figure 5. Calculated low enthalpy transition states for dihydropyridine reduction of a carbonyl compound.

requires the reaction to occur through a tilted-endo transition state. However, the same product can be formed through a parallel-exo transition state with the R groups reversed. Ohno's pre-transition state is still plausible if the magnesium is actually complexing both the dihydropyridine ring as well as the substrate carbonyl oxygen.

The possibility of a parallel-exo transition state was visualized by Kellogg in a macrocyclic chiral NAD(P)H model in which the magnesium ion would complex to the two amide carbonyls and an electron donation X group<sup>19</sup> (Figure 6). The carbonyl oxygen would also complex with the magnesium and the size of

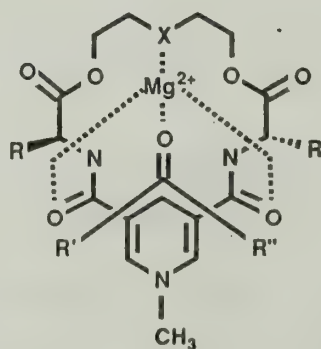


Figure 6. Kellogg's Chiral NAD(P)H Model: initially proposed ternary complex.

the R groups would control the configuration of the reduction product. Yet, the experimental results did not support the hypothesis (Table 2).

The fact that polymethylene bridged compounds reacted with comparable stereoselectivities to the ether bridged compounds suggested that complexation did not occur as predicted. From  $^{13}\text{C}$  NMR, it was found that the amide carbonyls contribute to complexation. Also, some of the macrocyclic compounds reduced activated ketones with high stereoselectivity. From the results, Kellogg proposed a ternary complex in which the magnesium ion is complexed to one amide carbonyl and to the substrate with the R and R' groups straddling

Table 2. Reduction of activated ketones by Chiral NAD(P)H Models.

R	X	R'	R''	conversion yield, (%)	product configuration	e.e. (%)
$-\text{CH}(\text{CH}_3)_2$	$-\text{O}-$	Ph	$\text{CO}_2\text{C}_2\text{H}_5$	80	S	86
"	$-\text{CH}_2-$	"	"	70	S	90
"	$-\text{O}-$	"	$\text{CO}_2(\text{CH}_2)_2\text{OCH}_3$	61	S	50
"	"	"	$\text{CF}_3$	58	S	60
$-\text{CH}_2\text{C}_6\text{H}_5$	"	"	$\text{CO}_2\text{C}_2\text{H}_5$	55	S	60

the R group on the model (Figure 7). This perpendicular approach of the substrate carbonyl was never considered by Ohno and coworkers but could easily explain their results as well.

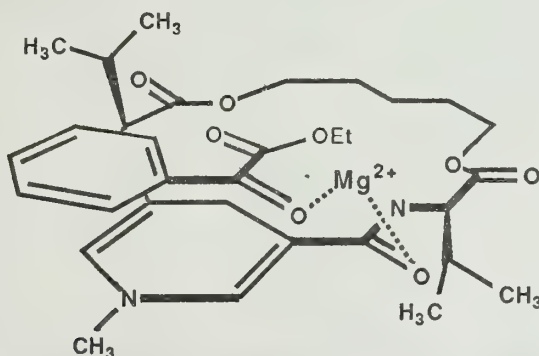
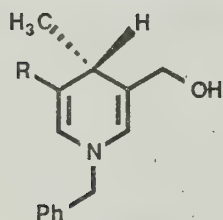


Figure 7. Kellogg's proposed transition state.

Recently, Meyers and coworkers<sup>20</sup> looked at the asymmetric reduction of methyl benzoylformate with chiral dihydropyridine derivatives containing the stereogenic center at the reaction site (Table 3).

Table 3. Reduction of ethyl benzoylformate with various Chiral NAD(P)H models.

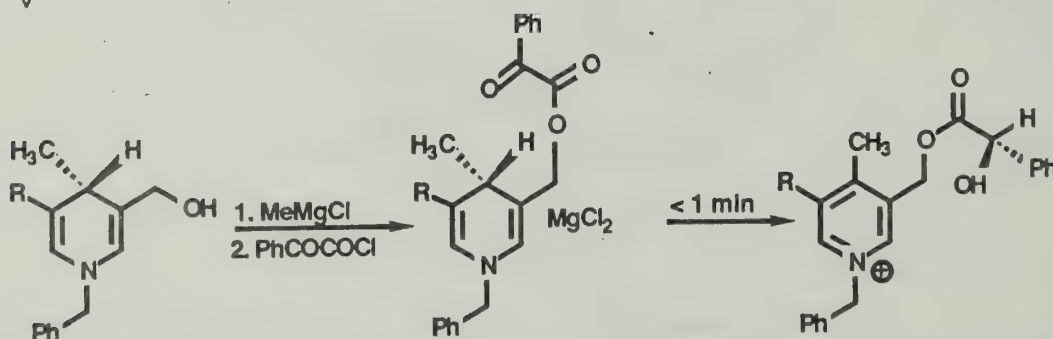


R	conversion (%)	e.e. (%)	product configuration
H	94	95	S
CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	61	91	S
CON(CH <sub>3</sub> ) <sub>2</sub>	98	62	R

Excellent enantioselectivity was obtained when R was hydrogen or carboethoxy. However, the asymmetric reduction dropped and the configuration was reversed when R was an amide group. The same trend was true when the hydroxyl moiety was replaced with a methoxy group. This indicates that the carbonyl of the ester group in the substrate interacts with the hydroxy and methoxy through non-bonding electron donation, and the hydroxy may also hydrogen bond to the ester. For the amide derivative, the reversed configuration of the product indicated that the ester group must be on the same side as the amide. This is due to the enhanced electron donating properties of the amide nitrogen toward the ester carbonyl. This result supports Ohno's conclusion that the most polar R group will be located on the same side as the dihydropyridine amide group.

Meyers also prepared a chiral NAD(P)H model in which an intramolecular asymmetric reduction occurs with a greater than 99 % asymmetric induction as well as an enhanced rate<sup>21</sup> (scheme V).

Scheme V



This was the highest asymmetric reduction and rate enhancement reported. After consideration of various transition states, Meyers proposed a ternary



complex in which the dihydropyridine ring is in a boat conformation and both carbonyls of the keto ester are complexed with the magnesium (Figure 8).

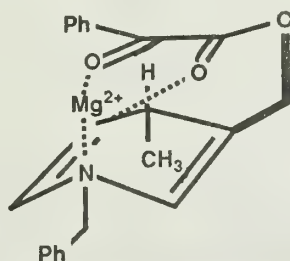


Figure 8. Meyer's proposed transition state.

Meyer's transition state raises the question of the preferred conformation of the dihydropyridine ring. Recent calculations<sup>22</sup> on the stability of the planar versus boat conformations indicate that the ring is quite flexible. Furthermore, stereoelectronic arguments predict that the boat conformation would be preferred due to the cis nitrogen lone pair of electrons ability to assist hydride departure. What effect this has on the stereospecificity is questionable.

The study of chiral NAD(P)H models has provided support for some of the important factors influencing this stereospecific enzyme reaction. The importance of an activating group such as a metal ion is quite evident from the results. Additionally, stereoelectronic factors are extremely important in determining the preferred ternary complex. Furthermore, the blocking of one face of the dihydropyridine ring has a significant role in determining the stereoselectivity in both the models and the enzyme reaction. Unfortunately, the use of chiral NAD(P)H models in asymmetric synthesis is not yet a reality due to their inability to reduce non-activated ketones. This is not unreasonable if one considers the substrates actually reduced by the enzymes. Refinement of these models may produce practical reagents for asymmetric reductions in the near future.

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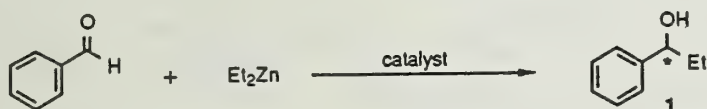


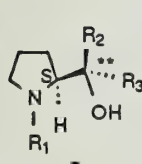
# CHIRAL CATALYSTS FOR THE ENANTIOSELECTIVE 1,2-ADDITION OF ORGANOZINC REAGENTS TO ALDEHYDES

Reported by John McCune

February 4, 1988

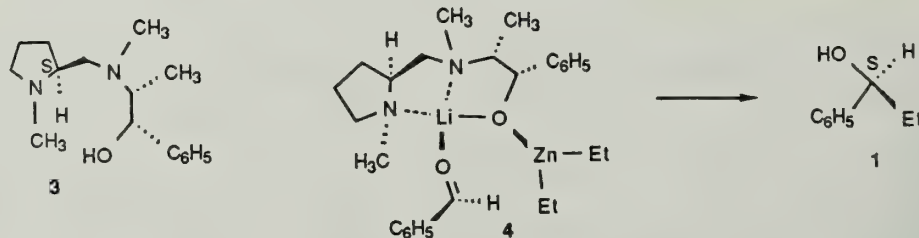
Optically active secondary alcohols are versatile synthetic intermediates. The asymmetric addition of organometallic reagents to aldehydes has been widely investigated. High enantiomeric excesses have been obtained using non-catalytic quantities of chiral auxiliaries at low reaction temperatures ( $< -100\text{ }^{\circ}\text{C}$ ).<sup>1</sup> Recent interest has centered on asymmetric induction in the addition of dialkylzinc reagents to aldehydes using chiral  $\beta$ -amino alcohols as catalysts.<sup>2</sup> The effectiveness of a chiral catalyst for enantioselectivity has been assigned by allowing benzaldehyde to react with diethylzinc in the presence of the catalyst to afford 1-phenylpropanol, **1**. Typically, an aldehyde:diethylzinc:catalyst molar ratio of 1:2.2:0.02 is allowed to stir at  $0\text{ }^{\circ}\text{C}$  in toluene or hexane for 24 hrs, and this is followed by an acid wash to remove catalyst.



	* *	$\text{R}_1$	$\text{R}_2$	$\text{R}_3$	*
					
2a	-	Me	Ph	Ph	S
2b	R	Me	Ph	H	R
2c	S	Me	H	Ph	S
2d	R	neopentyl	Ph	H	R
2e	S	neopentyl	H	Ph	R
2f	S	benzyl	H	Ph	R
2g	-	Me	H	H	-

Soai and co-workers have investigated the efficacy of a series of chiral pyrrolidinylmethanols, **2a-g**, as chiral catalysts. Catalyst **2d** gives (*R*)-**1**, in 100% enantiomeric excess (ee), 100% yield. Catalyst **2a** is complementary, affording (*S*)-**1** in 97% ee (100% yield). The nature of the alcohol substituent strongly influences asymmetric induction. In contrast to the tertiary alcohol **2a**, catalyst **2c**, a secondary alcohol, affords (*S*)-**1** in 31% ee and the primary alcohol **2g** fails to induce asymmetry. The stereochemistry of the carbinol asymmetric center and the size of the nitrogen substituent controls the sense of asymmetric induction. Bulky nitrogen substituents give enantioselectivity for the *R* isomers, 74% ee for (*R*)-**1** with **2b** compared to 100% ee for (*R*)-**1** with **2d**, and catalysts possessing *S* alcohols favor products with *S* stereochemistry, 31% ee for (*S*)-**1** with **2c**. Asymmetric induction is low when these two factors oppose each other, 3% ee for (*R*)-**1** with **2f** and 20% ee for (*R*)-**1** with **2e**. The enantioselectivities obtained with the lithium salts of **2a**, **2b** and **2d** are comparable to those with the parent catalysts.

Corey and Hannon report that the lithium salt of **3** gave (S)-**1** in 95% ee (68% yield).<sup>2b,c</sup> The reaction was presumed to proceed through complex **4**. This proposed intermediate unambiguously predicts the preferential transfer of ethyl to the si face of the formyl group to afford (S)-**1**, as observed.



Chiral  $\beta$ -amino alcohols are efficient catalysts for the reaction between a variety of other aldehydes and dialkylzincs. The reaction of diethylzinc with (E)-cinnamaldehyde gives the corresponding S alcohol in 97% ee (91% yield) when catalyzed by **2a**, and the R alcohol in 100% ee (89% yield) with **2d**. If heptanal is allowed to react with diethylzinc in the presence of **2a**, (S)-3-nonanol is obtained in 91% ee (96% yield). The reaction of di(n-butyl)zinc with benzaldehyde, catalyzed by the lithium salt of **3**, gives (S)-1-phenylpentanol in 84% ee (68% yield). A camphor-derived homochiral amino alcohol catalyzes the reaction of diethylzinc with 3-phenylpropanal to give the corresponding (S)-alcohol in 90% ee (80% yield).<sup>2e</sup>

In summary, several  $\beta$ -amino alcohols are effective catalysts for the enantioselective 1,2-addition of dialkylzinc reagents to aldehydes. Reaction conditions are mild and high enantiomeric excesses and chemical yields are obtained. This method is a practical and simple route to chiral secondary alcohols.

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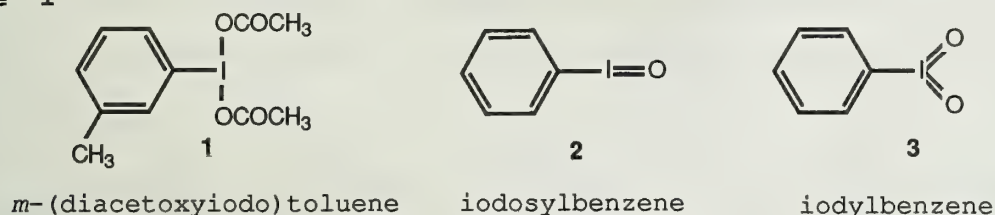
# RECENT APPLICATIONS OF HYPERVALENT IODINE IN ORGANIC SYNTHESIS

Reported by Aijun Liu

February 15, 1988

## INTRODUCTION

Hypervalent iodine compounds are those in which the iodine is in a higher oxidation state than the traditional -1 oxidation state (for examples, see Scheme I). The main bonding characteristic of iodine in Scheme I



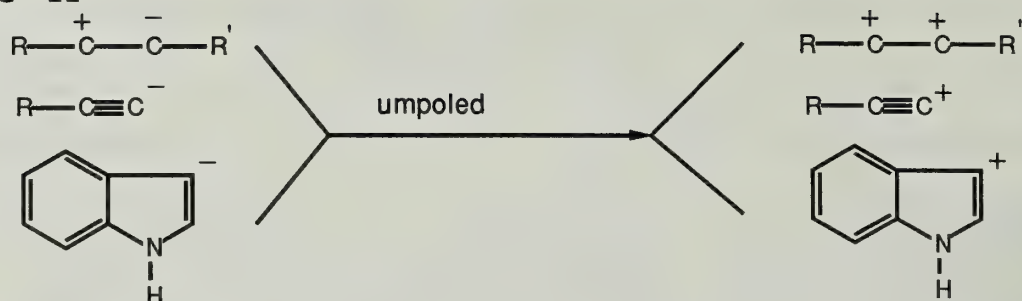
these compounds is that the occupied d orbitals participate in the hybridization. For example, in compound 1, iodine has a  $dsp^3$  hybridized structure with two lone pairs of electrons occupying two equatorial orbitals. One equatorial bond, two axial bonds and two coordinate iodine-oxygen bonds are oriented in a planar pentagon. This results in a T-shaped structure which has been verified by x-ray structure analysis.<sup>1</sup>

Even though one hypervalent iodine reagent, (dichloroiodo)benzene, was discovered in 1886,<sup>2</sup> these compounds have only been developed as useful synthetic reagents in the last two decades.<sup>3</sup> Because of their unique properties -- nontoxic nature, mild reaction conditions, adjustable reactivity, etc.-- they have been widely used and have a promising future in organic synthesis that can be seen from recent work.

## FORMATION OF UMPOLED SYNTHONS

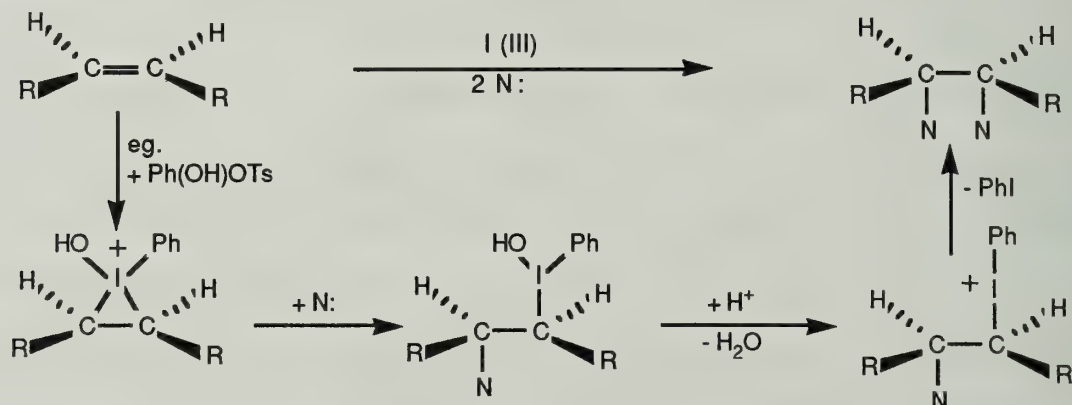
Hypervalent iodine reagents are good electrophilic species, while alkyl aryl iodonium salts are excellent for nucleophilic substitution; iodobenzene is a good leaving group even under the non-nucleophilic conditions. Therefore, (disubstitutediodo)benzene reagents can reverse the polarity of alkenes, terminal alkynes and the C-3 position of the indole nucleus (Scheme II) to enable these compounds to act as umpoled synthons, accepting nucleophilic attack at positions where electrophilic attack is normal.

Scheme II



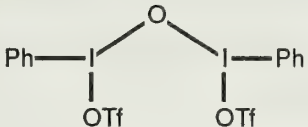
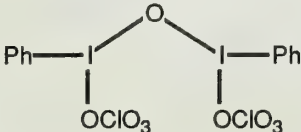
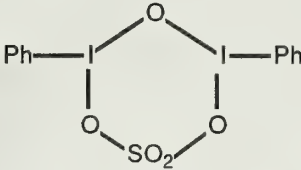
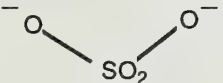
Umpoled synthons from alkenes produced through treatment with hypervalent iodine have been studied by several researchers,<sup>4</sup> who have developed new hypervalent iodine reagents and successfully introduced two nucleophilic groups on a double bond by this method (Scheme III). Mechanisms

Scheme III



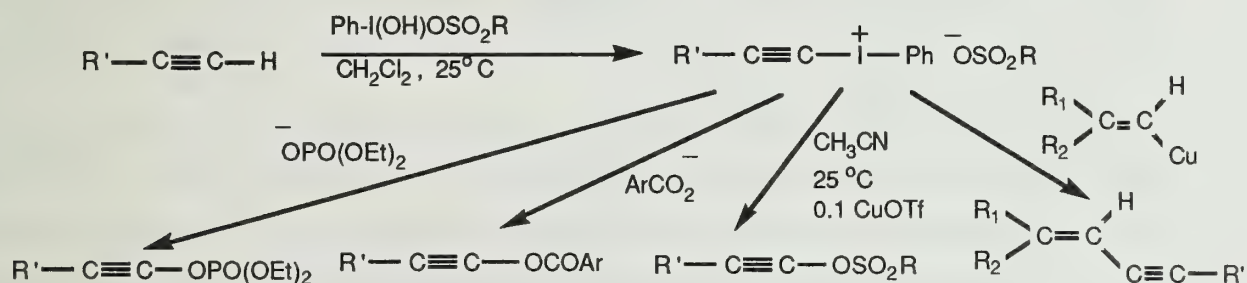
for this reaction are similar to the one shown in Scheme III. Interaction of the hypervalent iodine reagent with the alkene forms the cyclic organoiodine intermediate which undergoes the first  $S_N2$  substitution. The second  $S_N2$  substitution follows the generation of the iodonium salt and gives the product. The net result is the cis-addition of two nucleophilic groups because of the overall double inversion at carbons. Only in the case of the addition of sodium azide, with iodosylbenzene as the reagent, was a mixture of cis- and trans-addition products obtained. The reason may be that both  $S_N1$  and  $S_N2$  operate at the second substitution step. The hypervalent iodine reagents and nucleophiles that have been used in this reaction are presented in Table I. Obviously, this is a valuable synthetic route to 1,2-derivatives from olefins.

Table I. Reagents and Nucleophiles

I (III)	Ph-IO	$\begin{matrix} + \\ \text{Ph-I-O-BF}_3^- \end{matrix}$	
	Ph-I(OCOCH <sub>3</sub> ) <sub>2</sub>	$\begin{matrix} + \\ \text{Ph-I-ONO}_2^- \text{BF}_4^- \end{matrix}$	
	Ph-I(OCOCF <sub>3</sub> ) <sub>2</sub>	$\begin{matrix} + \\ \text{Ph-I-OSO}_2\text{O}^- \end{matrix}$	
	C <sub>3</sub> H <sub>7</sub> -I(OH)OTs		
	Ph-I(OH)OTs (Ms)		
	C <sub>3</sub> F <sub>7</sub> -I(OH)OTs		
N:	N <sub>3</sub> <sup>-</sup>	CF <sub>3</sub> COO <sup>-</sup>	TsO <sup>-</sup>
	ClO <sub>4</sub> <sup>-</sup>	CH <sub>3</sub> SO <sub>2</sub> O <sup>-</sup>	
	R'COO <sup>-</sup> (lactonization)		

It is well known that metallic salts which can accept electrophiles are easily formed from terminal alkynes. Hypervalent iodine reagents can be used to reverse this polarity. When terminal alkynes react with [hydroxy(tosyloxy)iodo]benzene, alkynylphenyliodonium sulfonates are produced in high yields. These species can undergo nucleophilic substitution, and the synthetically important alkynyl phosphates, carboxylates, tosylates and mesylates were first obtained by this method (Scheme IV).<sup>5</sup> Reaction of the alkynylphenyliodonium salts with vinyl copper reagents gives conjugated enynes with retention of the alkene geometry (Scheme IV).<sup>6</sup> When the terminal

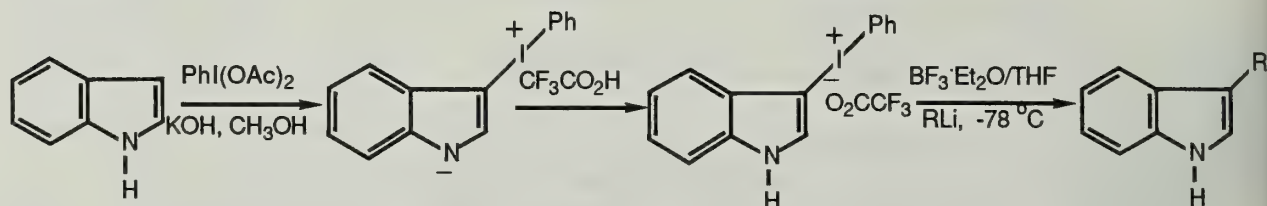
Scheme IV



alkynes reacted with [bis(trifluoroacetoxy)iodo]benzene and water,  $\alpha$ -hydroxy-ketones were formed in good yields because of the addition of water to alkynylphenyl-iodonium salts.<sup>7</sup>

The C-3 position of the indole nucleus usually undergoes enamine-type electrophilic reactions. With the help of hypervalent iodine reagents, nucleophilic substitution can occur at this position (Scheme V).<sup>8</sup>

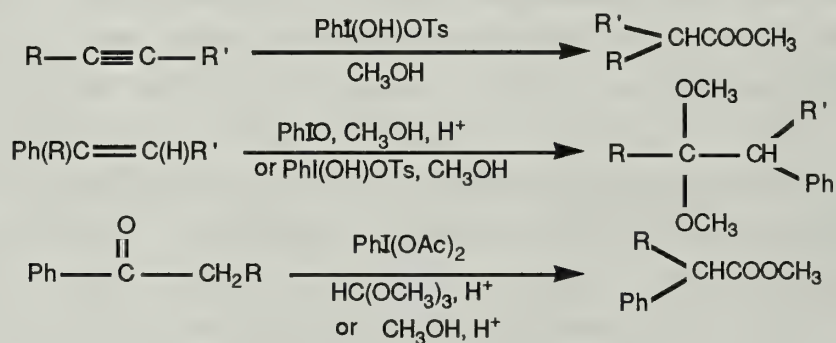
Scheme V



## REARRANGEMENT REACTIONS

The interaction of hypervalent iodine with aromatic alkenes, alkynes, ketones and amides can result in rearrangements, which can be divided into two categories: 1,2-migration and Hofmann-type degradation.

Scheme VI



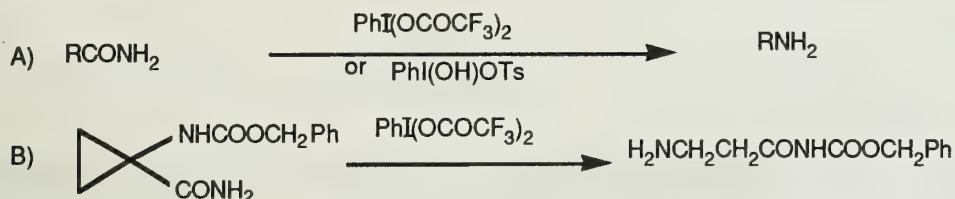
Moriarty<sup>9</sup> and Tamura<sup>10</sup> have reported that upon treatment with hypervalent iodine, aryl or alkyl groups in aromatic alkenes, alkynes and ketones underwent 1,2-migration to give ketals and esters (Scheme VI). High yields were achieved in the reactions, with aryl migration being more favorable than alkyl migration.

A rearrangement reaction, similar to the classical Hofmann degradation and yielding the corresponding amines, was observed when amides were treated with [bis(trifluoroacetoxy)iodo]benzene or [hydroxy(tosyloxy)iodo]benzene.<sup>11</sup> In this reaction, the configuration of the migrating group R is retained, as is the case in Hofmann degradation (Scheme VII-A). In order to verify the proposed mechanism, Koser isolated the N-(phenyliodonio)carboxamide tosylates, which gave the degradation products upon hydrolysis.<sup>12</sup> Interestingly, when Stammer carried out this reaction with the substrates N-(benzyloxycarbonyl)-1-aminocyclopropane-1-carboxamide, the rearrangement did



not give the desired amines but a ring opened degradation product (Scheme VII-B), resulting from a favored ring expansion assisted by the N-benzyloxycarbonylamino group and followed by ring opening and degradation.<sup>13</sup>

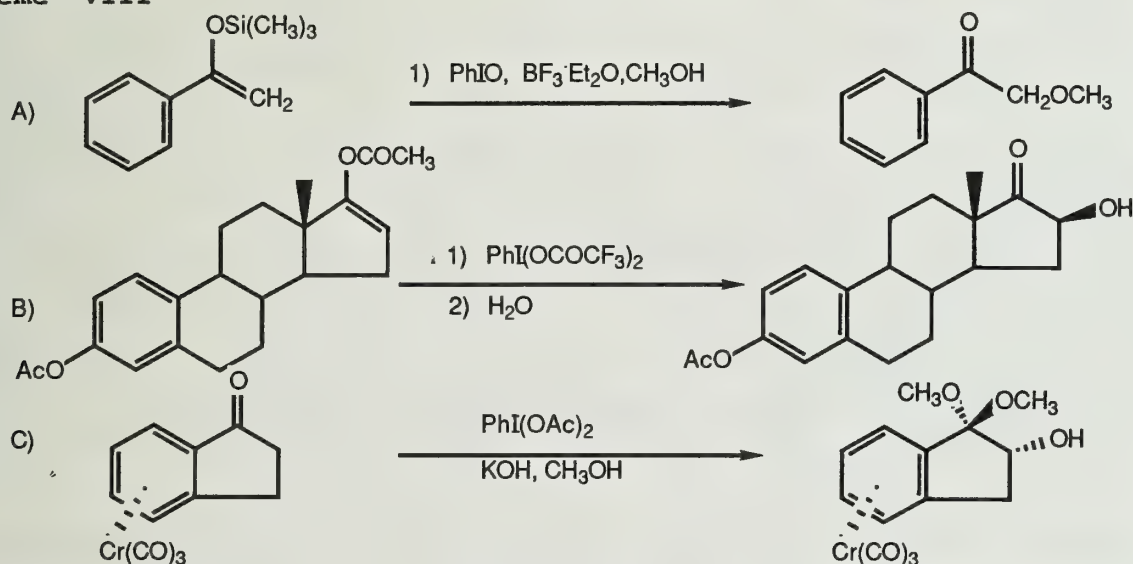
#### Scheme VII



#### REACTIONS THROUGH ENOL FORMS

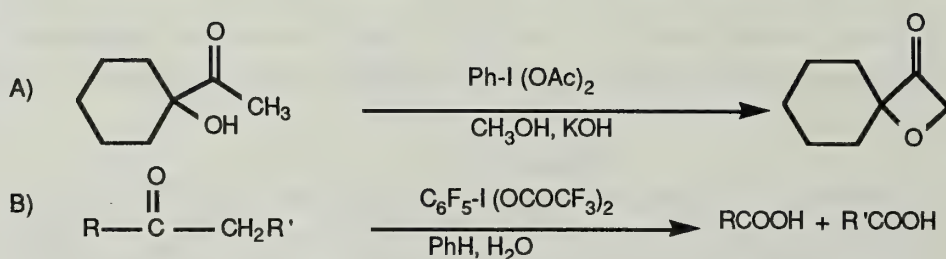
Typically, hypervalent iodine reagents react with enol acetates or enol silanes to form  $\alpha$ -hydroxy ketones; direct reaction with ketones through the enol tautomers forms  $\alpha$ -hydroxy dimethyl ketals. Furthermore, since hypervalent iodine reagents are large, these reactions can be quite stereoselective.

#### Scheme VIII



Some examples are presented in Scheme VIII.<sup>14</sup> In the direct oxidation of ketones, nitrosyl radical is not oxidized; this allows one to synthesize more functionalized spin labels.<sup>15</sup> Functionalization of ketones containing sensitive heterocycles such as epoxides, aziridines, and oxazolines is also possible, since these heterocycles are unaffected by the oxidants.<sup>16</sup> When treated with (diacetoxyiodo)benzene,  $\alpha$ -hydroxy ketones give oxetane-3-ones, which are important in biological studies and generally difficult to synthesize (Scheme IX-A).<sup>17</sup>

## Scheme IX



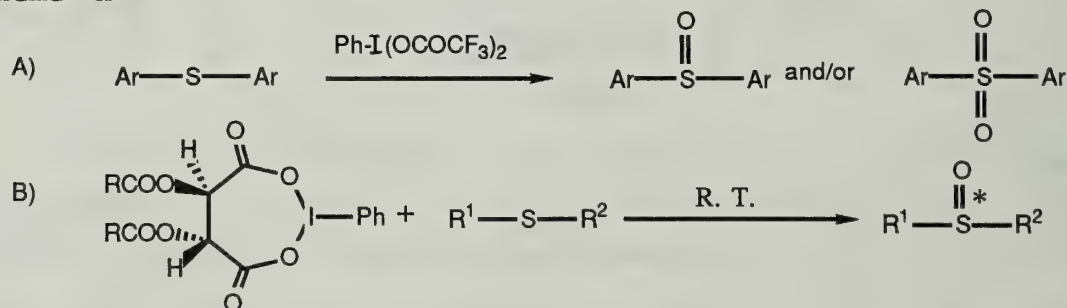
[Bis(trifluoroacetoxy)iodo]pentafluorobenzene is a stronger oxidizing reagent than [bis(trifluoroacetoxy)iodo]benzene. Upon treatment with this reagent in wet benzene, ketones are cleaved to acids (Scheme IX-B).<sup>18</sup>

## OXYGEN TRANSFER

Hypervalent iodine reagents are good oxygen atom donors. They can transfer oxygen under mild conditions to sulfides to give sulfoxides and/or sulfones, as well as to unsaturated bonds as ozone equivalents or epoxidation reagents.

[Bis(trifluoroacetoxy)iodo]benzene has been successfully used to oxidize aromatic sulfides to sulfoxides and/or sulfones in good yields (Scheme X-A).<sup>19</sup> However, when the same conditions are applied to alkyl

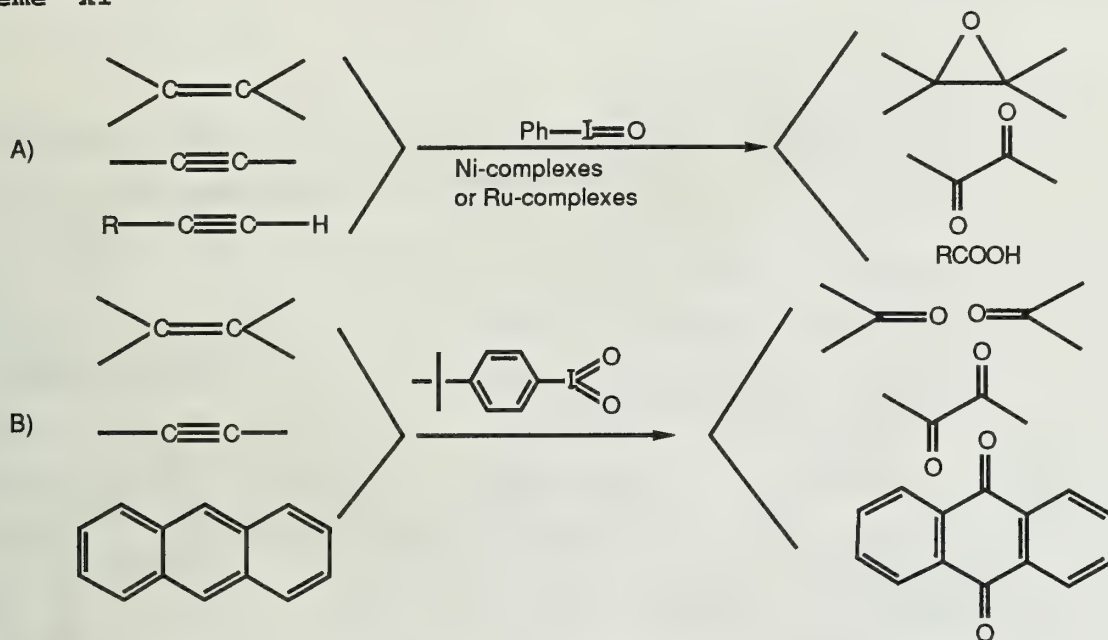
## Scheme X



sulfides, little of the corresponding sulfoxides or sulfones are found but many kinds of other products, including polymerisation products in some cases, are observed. Imamoto reported the first example of an asymmetric oxidation of sulfides by chiral hypervalent iodine (Scheme X-B).<sup>20</sup> He synthesized the chiral hypervalent reagents by the reaction of iodosylbenzene with derivatives of L-tartaric anhydride. In this reaction, cyclic chiral reagents gave much higher enantio-selectivity than noncyclic chiral reagents. Enantiomeric excesses of up to 53% were obtained, and the chemical yields were very good.

Iodosylbenzene and iodylbenzene are excellent epoxidation reagents and ozone equivalents. As shown by Kochi's <sup>21</sup> and Muller's <sup>22</sup> work, when nickel and ruthenium complexes are present as catalysts, iodosylbenzene transforms alkenes to epoxides and alkynes to diones or acids (Scheme XI-A).

**Scheme XI**



Ranganathan prepared a new iodylbenzene reagent, 4-t-butyliodoxybenzene, and used it as an ozone equivalent.<sup>23</sup> This reagent is very effective in transforming olefins, acetylenes and aromatic compounds into two moles of ketones and/or aldehydes, 1,2-diones and quinones, respectively (Scheme XI-B). This reagent also has the advantage that it can easily be dissolved in non-polar solvents and can, as well, be recovered and regenerated in high yield.

## MISCELLANEOUS

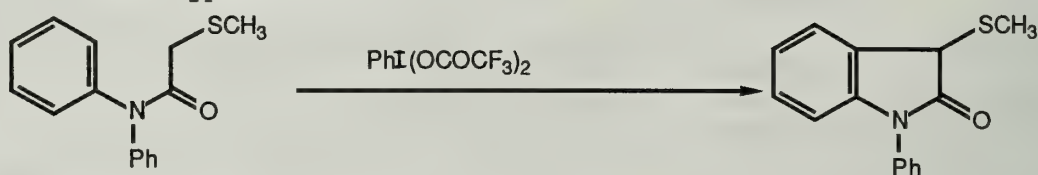
Pummerer-type reactions, nucleophilic substitutions and oxidative ring expansions can also be promoted by hypervalent iodine (for examples see Scheme XII).

Usually, Pummerer-type reactions of  $\alpha$ -acyl sulfides proceed in two steps, oxidation of sulfides to sulfoxides and electrophilic substitution under Pummerer reaction conditions. With [bis(trifluoroacetoxy)iodo]benzene, however, this type of reaction occurs in just one step via the Pummerer-type intermediates formed upon interaction of the reagent with the sulfur atom in  $\alpha$ -acyl sulfides (Scheme XII-A).<sup>24</sup>

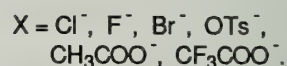
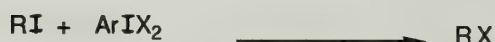
Nucleophilic substitution of alkyl iodides, assisted by hypervalent iodine via oxidative ligand transfer, is a valuable way to introduce the functional groups that are listed in Scheme XII under mild conditions and in good yields (Scheme XII-B).<sup>25</sup>

### Scheme XII

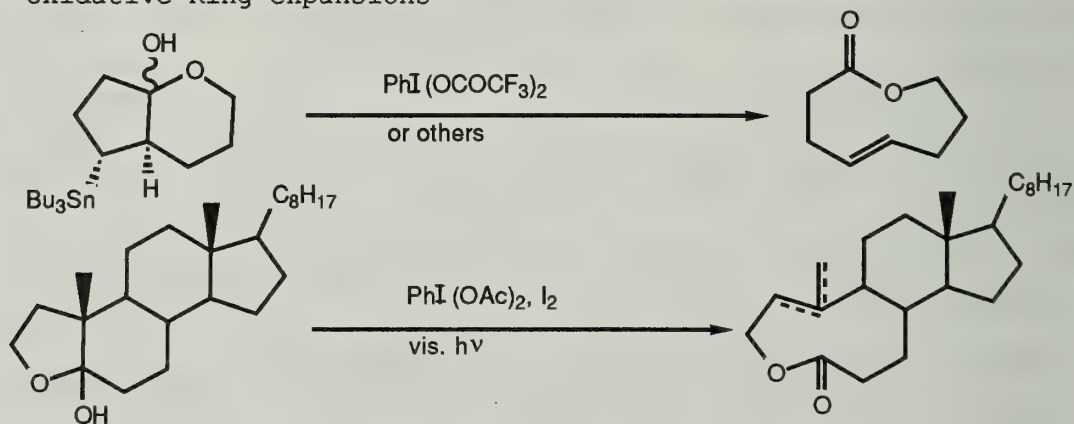
#### A) Pummerer-type Reactions



#### B) Nucleophilic Substitutions



#### C) Oxidative Ring expansions



Hypervalent iodine-induced oxidative ring expansion of lactols<sup>26</sup> and tributylstannyl lactols<sup>27</sup> provides a highly efficient route to medium-sized lactones. Radical and ionic mechanisms have been proposed for the lactonization of lactols and tributylstannyl lactols, respectively. In the ionic expansion reaction, stereospecific effects have been observed in which  $\alpha$ - or  $\beta$ -tributylstannyl compounds gave E or Z alkenic lactones, respectively (Scheme XII-C).

### CONCLUSION

Hypervalent iodine reagents can accomplish some important synthetic transformations efficiently, conveniently and under mild conditions. Even though they can interact with many kinds of functional groups and perform many types of reactions, it is possible to obtain high selectivity by control of media, time and temperature or by adjusting their reactivity through



changes in coordinating ligands. However, much work still remains to be done concerning their selectivity and capacity for chiral functionalization.

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# A SITE SPECIFIC DRUG DELIVERY SYSTEM BY THE PRODRUG APPROACH

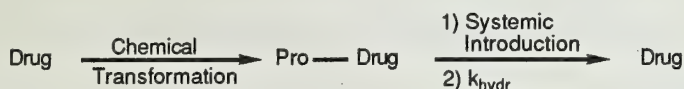
Reported by Andrew N. French

February 22, 1988

## INTRODUCTION

Improvements in drug delivery have been accomplished using a wide variety of methods, including liposomal<sup>1</sup> and micellar carriers,<sup>2</sup> ion exchange resins<sup>3</sup> and silicone bead impregnation.<sup>4</sup> A more flexible approach to drug delivery is through the judicious design of prodrugs. A prodrug is a chemically modified biologically active compound that displays different physico-chemical properties than the active compound. A prodrug should be stable in buffered solution, but readily revert to the starting drug, with appropriate kinetics in vivo (Scheme I).<sup>5</sup> Improvements in lipophilicity, solubility, aqueous stability,

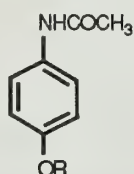
**Scheme I**



bioavailability, and toxicity have been made using the prodrug approach. Recently, a novel pro-moiety has been developed that provides site specific delivery of the drug to which it is attached, thus creating a chemical delivery system, the ultimate sort of prodrug.

## AMINO ACID PRODRUGS

Early work with drug delivery systems and the prodrug approach centered on the improvement of bioavailability.<sup>6</sup> Blocking of polar functional groups (OH, NH, COOH) with various ester-like functionalities proved successful in improving aqueous solubility and/or lipophilicity. Higuchi developed the amino acid ester pro-moiety for phenolic drugs and was able to show their effectiveness in systems like acetaminophen.<sup>7</sup>



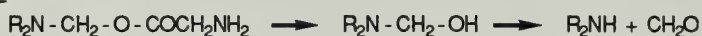
R = -H = acetamidophenol  
 -COCH<sub>2</sub>NH<sub>2</sub>  
 -COCH<sub>2</sub>CH(NH<sub>2</sub>)COOH  
 -COCH(NH<sub>2</sub>)CH<sub>2</sub>COOH

The rationale was that the different amino acids would enable the designer to select the desired solubility and hydrolytic properties of the prodrug. Moreover, the hydrolysis of amino acid esters is as likely to proceed by general bases as by enzymatic reactions. This

would provide for a rapid regeneration of the phenolic parent drug upon introduction.

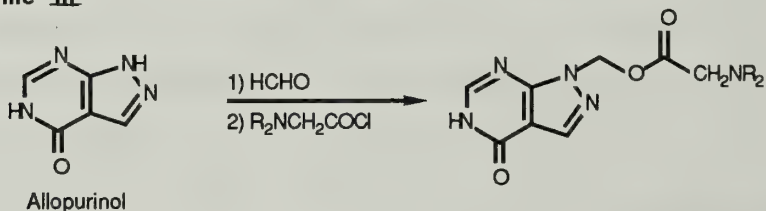
Bundgaard and Falch attempted to increase both aqueous solubility and lipophilicity of allopurinol by making N-acyl prodrugs.<sup>8</sup> They were successful to some degree in increasing both aqueous solubility and lipophilicity but the compounds could not be considered prodrugs due to their instability in solution. They were able to overcome the stability problem by making acyloxy amino acids of allopurinol.<sup>9</sup> The mechanism of release envisioned involves a rate determining enzymatic cleavage to give an unstable carbinolamine which eliminates the corresponding aldehyde and releases the free amine (Scheme II). This acyloxy group

#### Scheme II



is hydrolyzed more slowly and is more solution stable than the acyl derivative. The synthesis of the acyloxy amino acid involved reaction of the amine with the desired aldehyde, usually formaldehyde, followed by treatment with the desired acid halide (Scheme III). Bundgaard's

#### Scheme III

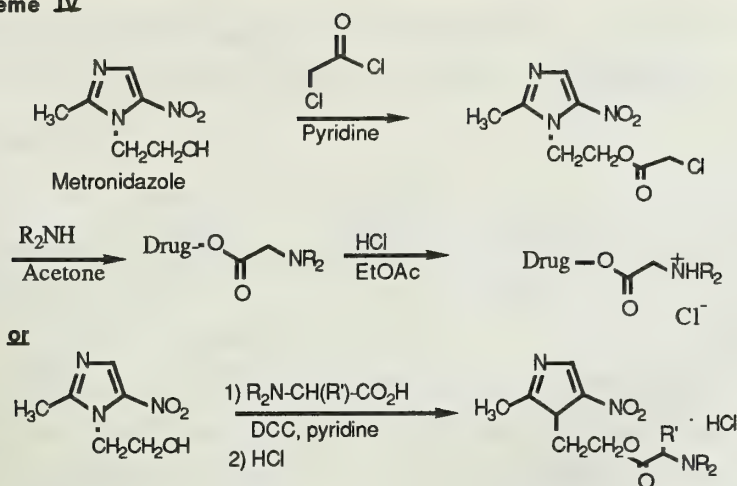


results show that his acyloxy amino acids are indeed more solution stable and are hydrolyzed readily in plasma.

Much research has been done to develop prodrugs of antimicrobial agents to improve their bioavailability. Bundgaard was able to overcome a solubility problem of metronidazole using Higuchi's amino acid esters.<sup>10</sup> Synthesis of the amino acid esters was accomplished by two routes. Reaction of metronidazole with the corresponding amino acid and dicyclohexylcarbodiimide in pyridine followed by addition to 3N hydrochloric acid in ethyl acetate gave the hydrochloride salt of the desired amino acid prodrug. An alternative route involved the formation of the haloacetate followed by reaction with the desired amine and salt formation with hydrochloric acid (Scheme IV). His amino acid prodrugs showed excellent stability in buffered solution and rapid hydrolysis in plasma.

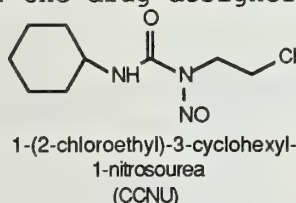


Scheme IV



### IMPROVEMENT OF SITE SPECIFICITY

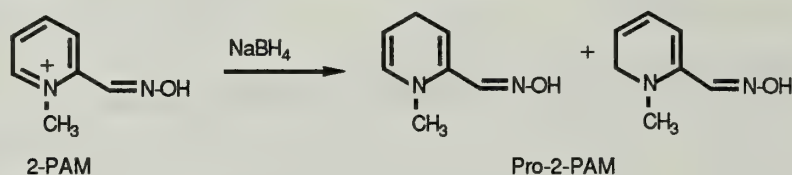
With the advent of new chemotherapeutic agents like CCNU, toxicity becomes a real concern for the drug designer. As most chemotherapeutic



agents are toxic to all cells, the need for site specificity arises as a new obstacle. The use of simple prodrug esters does not provide specificity because of the pervasiveness of esterase enzymes throughout the body. Thus new enzyme systems were targeted and the physiology of the desired site was considered.

Higuchi, in an effort to introduce an antitoxin across the blood brain barrier (BBB), exploited the enzymatic oxidation-reduction system in designing a prodrug of N-methylpyridinium-2-carbaldoxime salt (2-PAM), a known antitoxin for organophosphate poisoning.<sup>11</sup> Because 2-PAM is charged it cannot cross the lipophilic BBB. Direct intrathecal injection of the drug is not effective due to poor fluid circulation and slow diffusion through brain tissue. The possibility of infection or physical damage as a result of the injection is also a problem. Use of additional drugs to increase the permeability of the BBB was also attempted but proved to be too toxic. Previous analogues of 2-PAM, N-dodecylpyridinium-2-carbaldoxime salt among others, improved the lipophilicity but were not effective towards cholinesterase reactivation.<sup>12</sup>

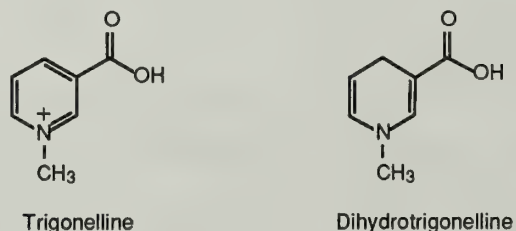
Higuchi solved the lipophilicity problem of 2-PAM by reducing 2-PAM to N-methyldihydropyridine-2-carbaldoxime (Scheme V).



This prodrug (Pro-2-PAM) was far more lipid soluble and was able to cross the BBB readily. Oxidation of Pro-2-PAM occurred readily and resulted in the desired drug 2-PAM. In vivo, the prodrug exhibited a halflife of 1.04 min. and showed a rapid distribution and oxidation to the pyridinium salt.<sup>11</sup> 2-PAM, when delivered as the prodrug proved very effective in reversing the anticholinesterase effects of organophosphate poisoning. The effectiveness with which the Pro-2-PAM/2-PAM system worked inspired Bodor to explore the dihydropyridine/pyridinium salt conversion as a potential pro-pro-moiety.

THE PYRIDINIUM SALT/ DIHYDROPYRIDINE PRO-MOIETY

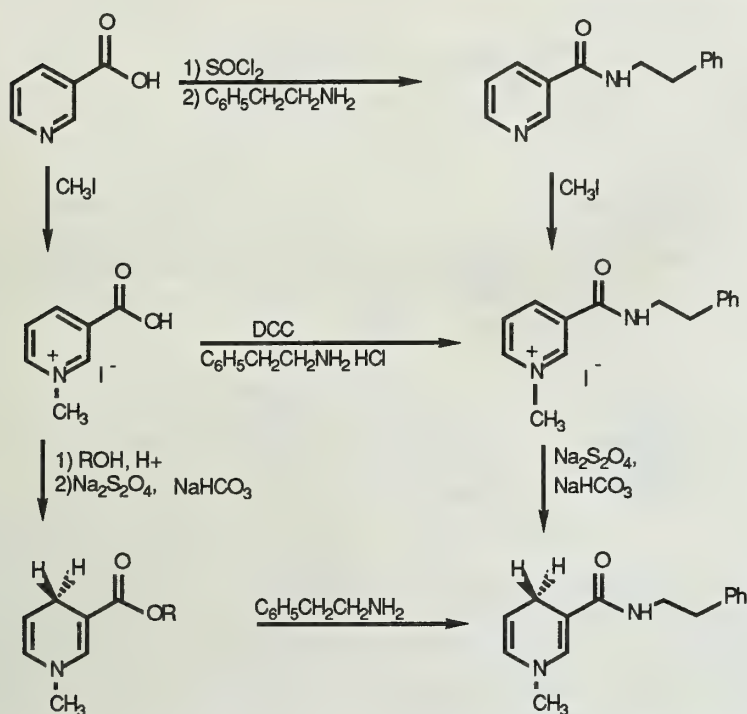
Bodor felt the use of the dihydropyridine/pyridinium salt promoiety would provide an additional feature to the design of prodrugs; that of site specificity. Bodor first chose to use trigonelline as the



pro-moiety and dihydrotrigonelline as the lipid soluble "pro-pro-moiety",<sup>13</sup> reasoning that the lipophilic dihydro form would readily pass through the BBB. Oxidation of the dihydro form to the pyridinium form would occur everywhere, resulting in the pyridinium form's being distributed throughout the body. The systemic pyridinium form would be rapidly removed from the body through the kidneys, due to its charged nature. The prodrug in the brain, however, once oxidized, would not be able to cross back through the BBB to be eliminated because of its charged character. Thus, a buildup of the pyridinium prodrug would be seen in the brain. Hydrolysis of the pro-moiety from the drug would then result in a sustained release of the drug to the brain. Bodor

first tried his theory using phenethylamine.<sup>14</sup> Synthesis of the prodrug can be envisioned by a variety of routes (Scheme VI).

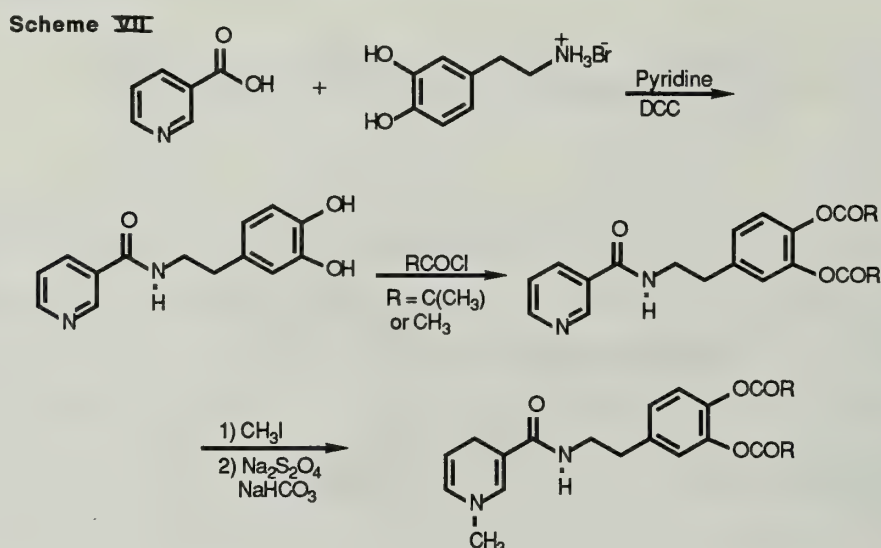
**Scheme VI**



The method of choice involved the reaction of phenethylamine with the acid chloride of nicotinic acid, followed by quaternization with methyl iodide and reduction of the pyridinium ring with sodium dithionite which gave the desired prodrug in 83% overall yield. In vitro studies showed the dihydropyridine prodrug having good stability in various tissue media. In vivo studies in rats showed a rapid loss of the prodrug from the blood and a rapid increase of the prodrug in the brain, peaking at ~20 min.. This was followed by a gradual loss (half life = 2.35h.) of prodrug concentration in the brain. The enzymatic cleavage of phenethylamine from the pyridinium pro-moiety occurred with a half life of three hours. All concentrations were determined by HPLC. Thus, Bodor's hypotheses proved correct for the phenethylamine study; the drug accumulated in the brain and was removed rapidly from the blood and surrounding tissues, the release of phenethylamine was steady and removal of the carrier from the brain was rapid.

Bodor's next study involved the prodrug of dopamine as a potentially better treatment of Parkinsonism. Bodor's prodrug modification of dopamine<sup>15</sup> involved the use of an additional protecting group to improve the lipophilicity of the catechol group. Studies by

Svensson showed the effectiveness of the pivalyl ester as a hydroxy pro-moiety.<sup>16</sup> The synthesis of the prodrug of dopamine was straightforward (Scheme VII). The prodrug demonstrated good in vitro stability. Results



of the in vivo studies were equally promising. Studies in rats again showed a rapid buildup of the prodrug in the brain with subsequent "lock in" following oxidation. The release of dopamine from the pyridinium salt could not be detected by the HPLC methods developed. It was demonstrated, using in vitro brain homogenates,<sup>17</sup> that the prodrug metabolized only to the desired dopamine and trigonelline, and not to other metabolites, suggesting the decrease in pyridinium prodrug concentration was a result of dopamine release. It was also suggested that the lack of a detectable increase of dopamine in the brain was a sign of slow hydrolysis of the pro-moiety relative to brain metabolism of dopamine. To test this hypothesis, a hormone inhibition study was conducted. It is known that dopamine inhibits prolactin secretion in the anterior pituitary. Thus, if dopamine is present, prolactin levels should decrease. Bodor's results determined that the introduction of dopamine prodrug resulted in a rapid and sustained reduction of prolactin indicating that the source of the prolactin inhibition was brain dopamine and not blood dopamine. It was also noted that the prodrug of dopamine does not itself inhibit prolactin secretion.

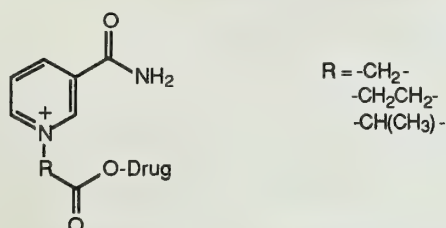
Bodor was also able to demonstrate the utility of this system by attaching it to steroids, testosterone and estradiol<sup>18</sup>, and showing that they, too, were transported selectively to the brain. This is



potentially useful for the regulation of reproductive function as well as certain behavioral traits.

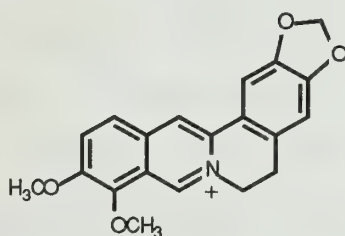
#### VARIATIONS ON THE DIHYDROPYRIDINE APPROACH

To expand the utility of the pyridinium/dihydropyridine pro-moiety, Bodor varied the position of attachment of the drug to the ring.<sup>19</sup> By attaching the drug to different positions of the pyridine ring, optimization of drug delivery could be achieved for different sorts of compounds. To vary the rates of hydrolysis of the pro-moiety from the parent drug, Bodor chose a series of N-substituents for the pyridinium ring and attached the drug to them, via an ester linkage.



Synthesis of these compounds involved reaction of the drug with the corresponding bromoalkyl acid chloride followed by coupling to nicotinimide to give the pyridinium compound. Reduction with basic sodium dithionite gave the dihydropyridine prodrug. His studies with steroid delivery using estradiol and testosterone showed that hydrolysis, and thus the level of drug maintained in the brain, was affected by the position of attachment.<sup>20</sup>

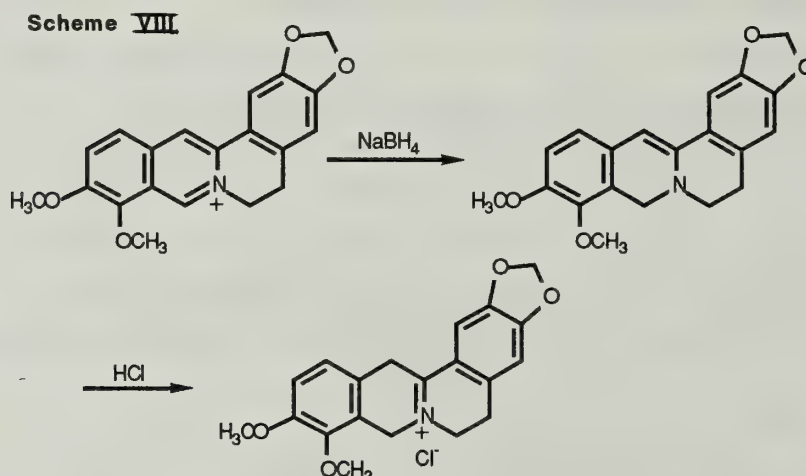
An additional way of using this pyridine/dihydropyridine system is with drugs that contain the pyridinium ring as part of its structure. This was tried for the drug berberine.<sup>21</sup>



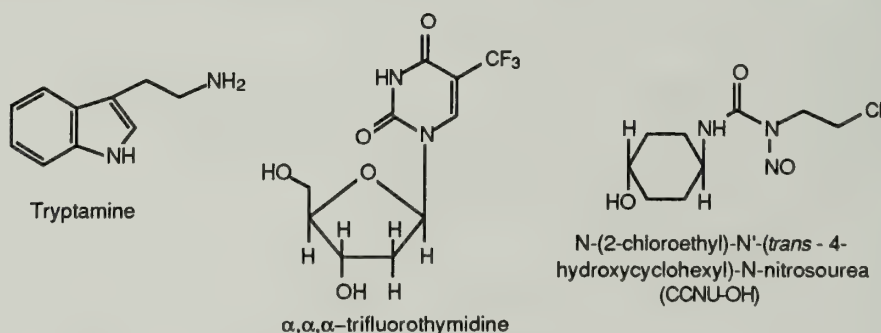
Berberine

This potent anti-tumor agent is believed to intercalate into DNA and has been shown to be toxic to certain lymphomas. In vivo, however, berberine is not active, presumably due to its inability to cross cell membranes. By reducing the pyridinium ring to the dihydro derivative, the lipophilicity should be increased. Bodor was able to increase the

lipophilicity by borohydride reduction followed by hydrochloric acid treatment to give the more stable iminium salt (Scheme VIII).



The dihydro compound had a rapid uptake in both the brain and the kidney. The halflife of berberine in the brain was approximately eleven hours, while the halflife in the rest of the body was very short, providing excellent site specific delivery of the drug to the brain. Thus, the toxicity of the drug is decreased everywhere except where the drug is needed. Other drugs are currently being tested to determine the generality of this pro-moiety. Recently, Bodor applied the pyridinium salt/dihydropyridine system to the delivery of tryptamine, a suspected



neurotransmitter responsible for serotonin release.<sup>22</sup> He also tried this system using the antiviral agent, trifluorothymidine.<sup>23</sup> His attempt with the antitumor agent, CCNU-OH,<sup>24</sup> proved to be less successful in providing brain specific delivery.

## CONCLUSION

The development of prodrugs has paralleled that of drug development. As new drugs are discovered and synthesized problems of

drug delivery will arise, requiring new pro-moieties to provide enhancements in lipophilicity, aqueous solubility and stability, toxicity and site specificity. The work by Higuchi, Bundgaard, and Bodor has provided chemists with a great deal of flexibility in drug design. With the development of site specific chemical delivery systems the work of the future must center on discovering new systems that will target other tissues and provide medicine with an expanded arsenal with which to fight disease.

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RECENT STUDIES ON THE MECHANISM OF THE DIELS-ALDER REACTION:  
IS IT SYNCHRONOUS OR TWO-STAGE?

Reported by Jean Schaap

February 25, 1988

The Diels-Alder reaction, first reported by Otto Diels and Kurt Alder in 1928,<sup>1</sup> involves the reaction of a diene with a dienophile to form two new  $\sigma$  bonds and a six-membered ring, with highly predictable regioselectivity and stereoselectivity. Since that time it has become one of the most important synthetic tools in organic chemistry. However, in spite of the fact that so much synthetic and mechanistic work has been done on the Diels-Alder reaction, its precise mechanism is still uncertain.<sup>2</sup>

PROPOSED MECHANISMS

Experimental evidence has shown that in most cases the thermal Diels-Alder is a concerted reaction; that is, it occurs in one kinetic step.<sup>3</sup> It falls into the class of pericyclic reactions, and so has long been considered by many chemists to be a synchronous process in which both new bonds are formed simultaneously. Since the bonds are assumed to be formed to the same extent in the transition state (1) it is symmetrical. Experimental evidence



1

to support this has included the stereospecificity of the reaction as well as kinetic and thermodynamic investigations. The selection rules developed by Woodward and Hoffmann in the 1960s<sup>4</sup> imply synchronicity and so have also fostered this assumption.

A two-step mechanism has also been considered, in order to explain substituent effects and regioselectivity. This would involve complete bond formation at one end first, with either a biradical or a zwitterionic intermediate (2), followed by formation of the second bond. A zwitterionic



2

intermediate is unlikely since absolute  $\rho$  values for Diels-Alder reactions are usually close to one and the rate generally shows little or no solvent dependence.<sup>2</sup> The biradical mechanism has fallen from favor except in certain cases in which steric factors or substituents cause the reaction to become nonstereospecific.

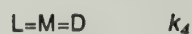
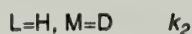
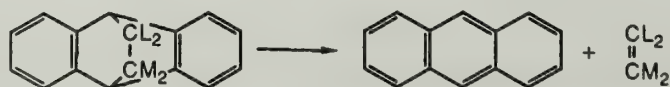
A third, intermediate mechanism was first proposed by Woodward and Katz in 1959.<sup>5</sup> They called this a two-stage mechanism, in which the two new bonds are both present in the transition state but one is formed to a greater extent than the other (an unsymmetrical transition state). This mechanism was introduced so that the concertedness, stereospecificity, and regioselectivity of the reaction could all be explained. The debate in the literature focuses on whether the mechanism of the Diels-Alder reaction is synchronous or two-stage. Much attention has been given to reactions involving symmetrical dienes and dienophiles, which are the cases which are most likely to be synchronous. There is some evidence that reactions which involve unsymmetrical dienes or dienophiles may go through unsymmetrical transition states.<sup>2,6</sup>

## EXPERIMENTAL STUDIES

### Isotope Effects

The precise structure of a transition state is difficult to determine experimentally; however, some methods have been introduced to attempt this in the case of the Diels-Alder reaction. In 1970, Taagepera and Thornton<sup>7</sup> reported the results of a study measuring secondary deuterium isotope effects observed in the retro Diels-Alder reaction of 9,10-dihydro-9,10-ethanoanthracene and its di- and tetra-deuterated analogs (see Scheme I).

Scheme I.



The rate constants for these reactions are  $k_0$ ,  $k_2$ , and  $k_4$ , respectively. For a completely symmetrical transition state

$$(k_2/k_0)^2 = k_4/k_0, \quad (1)$$

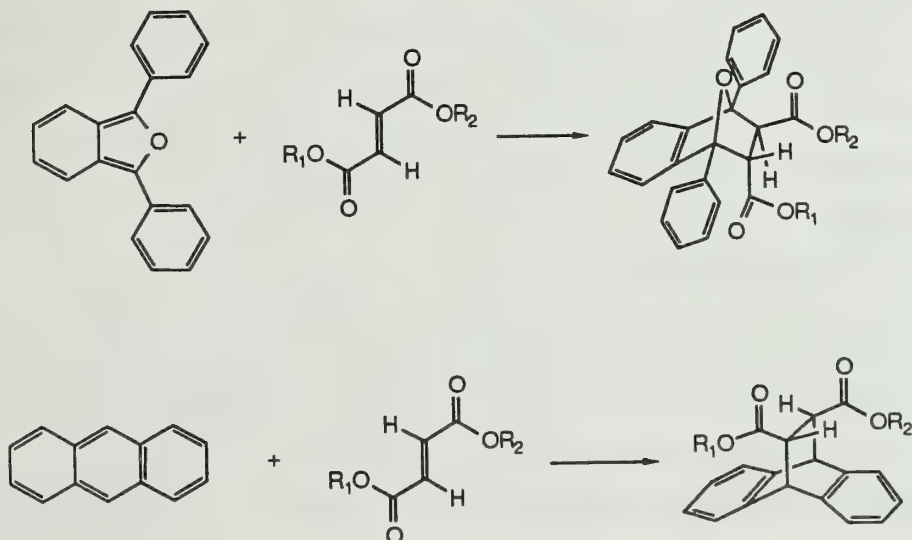
while for a stepwise transition state where one bond is broken first,

$$k_4/k_0 = (2k_2/k_0) - 1. \quad (2)$$

A value between these would be expected for an intermediate mechanism. The measured rate ratios fit Equation 1, indicating that the mechanism took place through a symmetrical transition state, with both bonds broken to the same extent. This method, however, is not easily applicable because secondary kinetic isotope effects are so small that the error inherent in the experimental method may obscure the differences expected for different transition states.

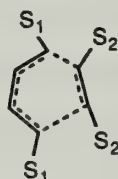
### Cooperativity in Asymmetric Induction

Another experimental method for determining the nature of the transition state was introduced by Tolbert.<sup>8</sup> It is based on the principle of asymmetric induction by a chiral group attached to the diene. If a transition state is symmetrical, two chiral groups, one at each end of the diene, should display cooperativity with respect to asymmetric induction. Thus, in a symmetrical transition state the ratio of diastereomers produced with two chiral auxiliaries will be the square of the ratio with one chiral auxiliary. Tolbert tested his hypothesis, choosing chiral groups which would give only a minimal steric interaction and no electronic perturbation. The reactions of 1,3-diphenylisobenzofuran with dimethyl, methyl (-)-bornyl, and di-(-)-bornyl fumarate, and anthracene with dimethyl, methyl (-)-bornyl, di-(-)-bornyl, methyl (-)-menthyl, and di-(-)-menthyl fumarate were examined (see Scheme II), and in each case cooperativity was observed. Tolbert interpreted this



as proof that the transition state is symmetrical, with each of the two new bonds formed to the same extent. However, this assumption that cooperativity is proof of a synchronous mechanism has been challenged by Dewar.<sup>3</sup> He argues that since the bond lengths in the newly forming bonds are directly related to the hybridization of the carbons at each end, it is possible for groups to be the same distance apart, thus producing the same steric interactions, while being connected by bonds of widely differing length (see Scheme III). Because of this, a lack of cooperativity can be used to rule out a symmetrical transition state, but cooperativity cannot be used as proof for a symmetrical transition state and synchronous mechanism.

**Scheme III.** A transition state with different bond lengths but equal distances between the bulky groups at each end of the reacting molecules.



### Retention of Stereochemistry

Other experimental work by Houk<sup>9</sup> shows that a diradical intermediate is unlikely, at least in the case of butadiene and ethylene. Houk studied the reaction of 1,1,4,4-tetradeuterio-1,3-butadiene with *cis*- or *trans*-1,2-dideuterioethylene. At 185 °C no scrambling of stereochemistry was seen, with a level of detection of 1%. This indicates that no diradical intermediate is formed, since the barrier to rotation around the single bond of a primary radical is only 0.0-0.4 kcal/mol. If the energy required for bond rotation were 0.4 kcal/mol greater than that for collapse to cyclohexene product, the reaction should be only 22% stereospecific at 185 °C. To achieve less than 1% scrambling a difference of at least 3.7 kcal/mol is required.

### THEORETICAL STUDIES

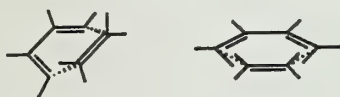
Because of the elusive nature of the transition state and the difficulties in interpreting experimental evidence, much theoretical work has been done in this area. Both semi-empirical and *ab initio* calculations have been used, often leading to very different transition state structures and mechanisms. This has caused a great deal of controversy over the usefulness and validity of different calculational methods.



### Ab Initio Studies

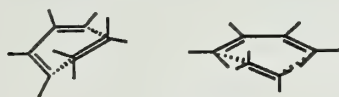
Several calculations, mainly those using *ab initio* methods, have supported synchronous or nearly synchronous mechanisms. Houk studied the reaction of butadiene with ethylene using *ab initio* calculations and the STO-3G basis set.<sup>10</sup> After optimizing all variables, he found a transition structure with  $C_s$  symmetry and forming bond lengths of 2.217 Å (see Scheme IV). It had one imaginary vibrational frequency, showing that it was a true transition structure. An activation energy of 32.7 kcal/mol was calculated (experimental value = 27.5 kcal/mol<sup>11</sup>). Restricted Hartree-Fock (RHF) calculations were also done using the STO-3G and 3-21G basis sets; these also supported a synchronous mechanism.<sup>9</sup> However, electron correlation was not included in these calculations.

**Scheme IV.** Two views of a transition structure with  $C_s$  symmetry.



Burke and co-workers<sup>13</sup> studied the reaction of butadiene and ethylene with *ab initio* calculations using the STO-3G and 7s-3p basis sets. After full geometry optimization, they found a transition state of  $C_1$  symmetry (see Scheme V). This transition structure was 1.2 kcal/mol lower in energy than

**Scheme V.** Two views of a transition structure with  $C_1$  symmetry.



the corresponding boatlike transition structure and lead to a product cyclohexene in a conformation closer to the more stable half-chair configuration. The lengths for the forming bonds were found to be  $2.26 \pm 0.02$  Å. The tendency towards asynchronism (A) was calculated using the method of Leroy and Sana<sup>14</sup> in which the two forming bonds are constrained to be the same length and the bond populations are measured and compared. A was found to be only 2.8%. Burke reasoned that the only Diels-Alder reactions which might be absolutely synchronous would be those that are confined to strict  $C_s$  symmetry and therefore must go through a boatlike transition structure. He studied the reactions of ethylene with cyclopentadiene and furan using *ab initio* calculations and the STO-3G, 3-21G, and 4-31G basis sets, and found

symmetrical  $C_s$  transition structures for both of these reactions.<sup>13d</sup> No tendency towards asynchronism was found. When a substituent was placed on either the diene or the dienophile, however, a tendency towards asynchronism was always seen. However, correlation energy was not included in these calculations either.

Bernardi and co-workers also studied the reaction of ethylene and butadiene using *ab initio* calculations.<sup>12</sup> Transition structures were located using the STO-3G basis set, including electron correlation using the Complete Active Space Self-Consistent Field (CASSCF) method. One synchronous transition structure with  $C_s$  symmetry was located; three asynchronous transition structures which differed in the relative conformations of the reactants were also found. When the larger split-valence 4-31G basis set was used for calculations, however, only the synchronous transition structure could be found.

#### Semi-empirical studies

Other calculations, particularly those using semi-empirical techniques, have produced unsymmetrical transition structures corresponding to two-stage mechanisms. Dewar and co-workers<sup>15</sup> studied the reaction of butadiene and ethylene and the retro Diels-Alder reaction of cyclohexene using MINDO/3 and including CI. The predicted mechanism showed a first transition state, a biradicaloid intermediate, and a second transition state which corresponded to the rate-limiting step of the reaction (see Fig. 1). This second

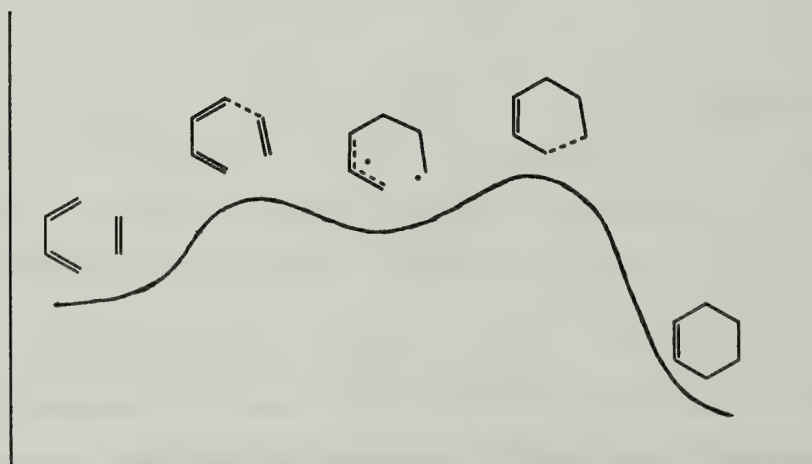


Figure 1. The MINDO/3 predicted reaction coordinate diagram.

transition structure was found to be very unsymmetrical, with one bond almost completely formed and the other still very weak. Dewar described the biradicaloid as a singlet closed-shell species with weak interaction between the biradical centers which would lead to retention of stereochemistry and an energy of activation for closure.<sup>3</sup> Further studies using MNDO and AM1 including CI and also calculating the reactions between butadiene and various cyano-substituted ethylenes led to similar predicted mechanisms and unsymmetrical transition structures.<sup>16</sup> However, since the parameters used in MINDO/3 and MNDO automatically include electron correlation, when CI is included the energies predicted for biradicals are 20-25 kcal/mol too low. When this is taken into consideration, the first transition state and intermediate disappear and the second transition state becomes the overall transition state for the reaction. Dewar concludes that the transition structures for all of the cyano-substituted ethylenes are unsymmetrical, but that there is not enough evidence to determine the mechanism in the case of butadiene and ethylene. Calculations by Jug on the reaction of butadiene and ethylene using SINDO1 also resulted in a highly unsymmetrical transition structure with important diradical character.<sup>17</sup>

#### CRITICISMS OF THEORETICAL METHODS

Several theories have been proposed to explain the different transition structures obtained using *ab initio* and semi-empirical calculations. The first, proposed by Basilevsky<sup>18</sup> and Houk,<sup>19</sup> is that semi-empirical methods such as CNDO and MINDO use the zero differential overlap (ZDO) approximation, while *ab initio* methods take differential overlap into account. Overlap of filled orbitals causes destabilization, and this destabilization is greater for unsymmetrical transition states. Thus, when differential overlap is ignored, a preference for asynchronous mechanisms appears. Dewar<sup>15b</sup> rejects this argument for MINDO-type methods because they use parameters which reproduce experimental data and so should compensate for these errors. However, these parameters are chosen using experimental data such as heats of formation for molecules and it is not known whether these parameters from molecular ground states are valid for transition state structures.<sup>19</sup>

Dewar notes<sup>16</sup> that both MINDO and MINDO/3 tend to overestimate repulsive interactions between atoms when the distance between them is 1.5-2 times the distance of a covalent bond. Since the lengths of the forming bonds in the symmetrical Diels-Alder transition structure fall into this region, these



calculational methods show a preference for highly unsymmetrical transition structures. However, he claims that since his calculations use Unrestricted Hartree-Fock (UHF) theory they are more accurate than those of Houk, who uses RHF in his calculations. Dewar claims that RHF gives energies for biradicals which are too high, and AM1 calculations using RHF predicted a symmetrical transition structure for the reaction of butadiene and ethylene.<sup>16</sup> Houk, on the other hand, argues that UHF calculations are biased towards biradicals because the wavefunction used is about 50% triplet.

Another explanation for the different calculated transition structures has been proposed by M. Ortega and co-workers.<sup>20</sup> This is a difference in correlation energy, which is included in the MINDO/3 parameterization, but which has to be specifically included in *ab initio* calculations. Correlation energy increases in importance as frontier orbitals become closer in energy and also as a structure shows greater electronic localization. Since both of these are features of the unsymmetrical transition state, the inclusion of correlation energy is expected to preferentially stabilize an asynchronous mechanism. Ortega demonstrates this preferential stabilization by *ab initio* calculations using the STO-3G basis set and the Møller-Plesset method for including electron correlation. However, since Bernardi included extensive electron correlation in his calculations, it is unlikely that this can fully explain the different results obtained using *ab initio* and semi-empirical methods.

## CONCLUSION

Experimental studies<sup>7-9</sup> and the best *ab initio* studies carried out to date<sup>12</sup> indicate that the reaction between symmetrical dienes and dienophiles is synchronous. Much less work has been done on unsymmetrical systems, although certain studies suggest that some degree of asymmetry may exist in these transition states.<sup>6,13</sup>

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## CHIRAL IRON ACYL COMPOUNDS IN ORGANIC SYNTHESIS

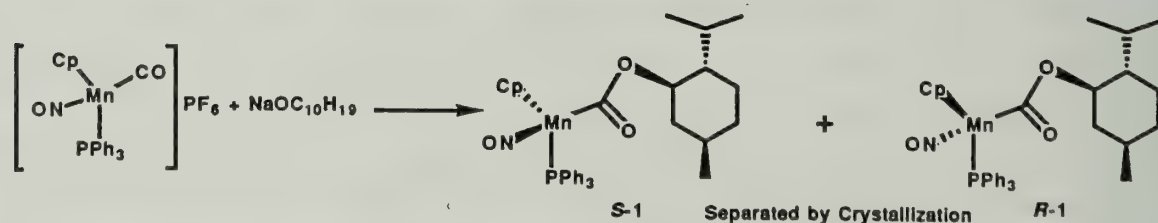
Reported by James P. Edwards

March 7, 1988

## INTRODUCTION

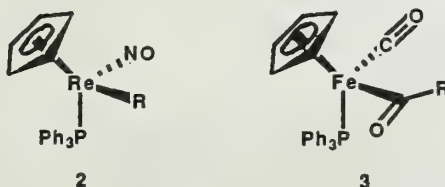
The subjects of chirality and asymmetric synthesis have a long and rich history in organic chemistry,<sup>1</sup> both in the synthesis of natural products and new and interesting biologically active compounds,<sup>2</sup> and in the study of reaction mechanisms.<sup>3</sup> In inorganic and organometallic chemistry, these subjects have only recently begun to come under intense investigation, but the advances have been dramatic.<sup>4</sup> Of particular interest to organic chemists is the application of chiral organometallic species to asymmetric organic reactions. Metallic reagents and catalysts that are chiral due to the presence of chiral organic ligands or chelants are quite well known.<sup>4b</sup> For example, there is a myriad of chiral ligands that have been employed as asymmetric hydrogenation catalysts,<sup>5</sup> and the famed Sharpless asymmetric epoxidation employs an *in situ*-generated chiral titanium complex to achieve its high enantioselectivity.<sup>6</sup> However, chiral metal complexes in which the metal atom is the sole stereogenic center are much scarcer. The first resolution of a chiral metal compound with a stereogenic metal atom was achieved by Henri Brunner in 1969,<sup>7</sup> who resolved, but did not assign the absolute configuration to, the chiral manganese compound 1 utilizing enantiomerically pure (-)-menthol (Scheme I). This compound was not configurationally stable at the metal center and epimerized readily upon warming in solution.

Scheme I



Chiral metal compounds stereogenic solely at the metal atom which have applications in asymmetric organic synthesis are scarcer still,<sup>4b</sup> but two notable examples are the chiral rhenium alkyl compounds 2, the chemistry of which has been pioneered by Gladysz,<sup>8</sup> and the chiral iron acyl compounds 3, studied intensively by Davies<sup>9-12</sup> and Liebeskind.<sup>13</sup> The parent iron acyl

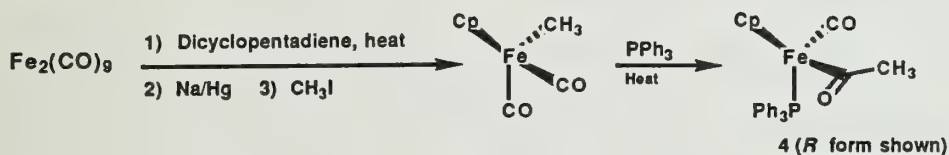
compound 4 is now commercially available in both racemic and enantiomerically pure forms.<sup>14</sup> The chemistry of these chiral iron acyl compounds, including synthesis, resolution, asymmetric bond forming reactions at the acyl ligand, and theoretical and conformational studies, is the subject of this report.



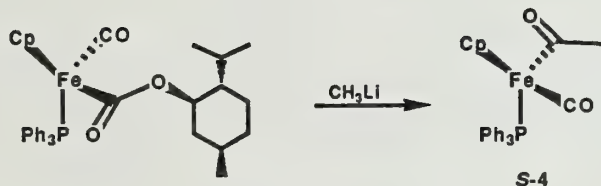
## SYNTHESIS AND STRUCTURE OF IRON ACYL COMPOUNDS

The air-stable iron acyl complex 4 is easily prepared in three steps from diiron nonacarbonyl (Scheme II).<sup>15</sup> The absolute configurations of (-) and (+) 4 have been unambiguously assigned as *R* and *S*,<sup>†</sup> respectively, by Davies.<sup>11c</sup> The enantiomeric purity of optically active samples of 4 can be assessed by the use of the chiral shift reagent (Eu(tfc)<sub>3</sub>).<sup>11c</sup> Compound 4 was first obtained in enantiomerically pure form by Brunner,<sup>18</sup> using a method similar to that used in the resolution of 1 (Scheme III).

Scheme II



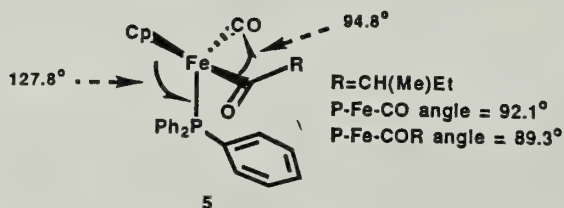
Scheme III



Iron acyl compounds 3 and related species 2 have been described as both pseudotetrahedral<sup>8,13,17</sup> and pseudooctahedral,<sup>9-12,19</sup> but it is clear from crystal structure data that these species are pseudooctahedral,<sup>11e</sup> with

<sup>†</sup> The Stanley and Baird<sup>16</sup> modification of the CIP<sup>17</sup> rules for assigning absolute configurations at metal centers has been generally used for organometallic species.<sup>8,9,13</sup> The sum of the molecular weights of all atoms bonded to the metal atom is considered to be the molecular weight of polyhapto ligands. C<sub>5</sub>H<sub>5</sub> then has a "molecular weight" of 60, and ligand priority order for 4 is C<sub>5</sub>H<sub>5</sub>>PPh<sub>3</sub>>CO>COMe.

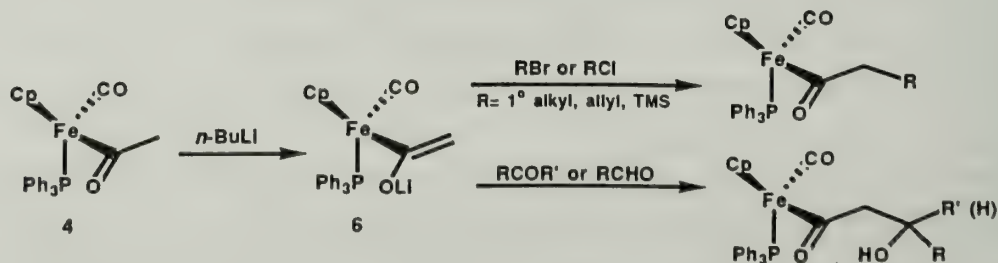
typical P-M-CO(NO), P-M-COR(R), and CO(NO)-M-COR(R) bond angles of 85-98°. The bond angle P-M-Cp, where Cp is defined as the centroid of the cyclopentadienyl ring, is generally 119-129°. The Cp ring thus occupies the equivalent of three coordination sites on the octahedron. The values shown for compound 5 are typical.<sup>9m</sup> These data are more consistent with a pseudooctahedral structure rather than a pseudotetrahedral structure.



### REACTIVITY OF IRON ACYL ENOLATES

Compound 4 has many potential sites of reactivity: all seven carbon atoms attached to the iron atom are potentially electrophilic and the iron atom itself is potentially nucleophilic. However, the enolate 6 can be easily generated by treatment of a cold (-78 °C) tetrahydrofuran (THF) solution of 4 with lithium diisopropylamide (LDA)<sup>9n,13f</sup> or *n*-butyllithium (*n*-BuLi).<sup>9n</sup> Note that *n*-BuLi deprotonates 4 and no addition to either carbonyl or the Cp ring is observed. Surprisingly, only recently has the acidic nature of the  $\alpha$ -carbon hydrogens of metal acyl compounds been investigated. Davies'<sup>9n</sup> and Liebeskind's<sup>13f</sup> reports of enolates derived from metal acyls were preceded only by Bergman's 1982 report<sup>20</sup> of the generation and reaction of enolates derived from cobaltacyclopentanones. The enolate 6 can be alkylated at the  $\alpha$ -carbon with various alkyl iodides and allyl, propargyl, and benzyl bromides in moderate to high yields.<sup>9n,13f</sup> Interestingly, trimethylsilyl chloride (TMSCl) silylates the  $\alpha$ -carbon rather than the carbonyl oxygen.<sup>9n</sup> Enolate 6 also undergoes aldol condensations with aldehydes and ketones (Scheme IV).<sup>9n,13f</sup>

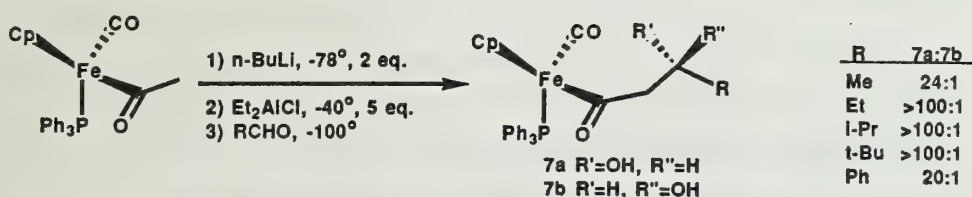
Scheme IV



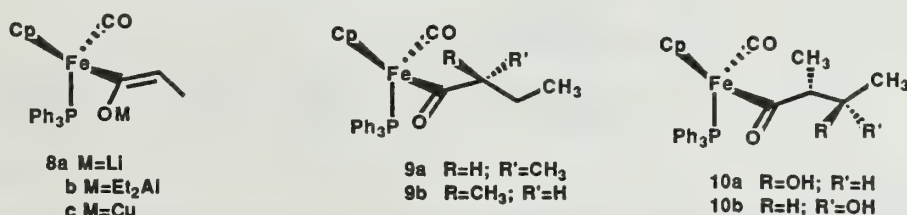


Reactions with aldehydes showed little stereoselectivity initially, but the use of copper or aluminum enolates improved the selectivity dramatically.<sup>9c,j;13a,d</sup> The conditions necessary for excellent selectivities are crucial:<sup>13a</sup> best results are obtained by the use of 2 eq. of *n*-BuLi and 5 eq. of diethylaluminum chloride (Et<sub>2</sub>AlCl),<sup>9j</sup> allowing transmetalation to occur by warming to -40 °C for 45 minutes, followed by addition of the aldehyde as a THF solution at -100 °C. Diastereoselectivities of 20:1 (benzaldehyde) to >100:1 (pivalaldehyde) are achieved, favoring diastereomer **7a** over **7b**, in 85-90% yield (Scheme V).<sup>9j</sup> Treatment of the resulting acyl complexes with bromine (Br<sub>2</sub>)<sup>9f,h,n</sup> or *N*-bromo succinimide (NBS)<sup>13a,d,f</sup> in alcoholic solvents afforded the corresponding esters in high yield. Thus, the aluminum enolate corresponding to **6** is an efficient equivalent of a chiral acetate enolate.

Scheme V



The enolates of more highly substituted iron acyl complexes, e.g. **8a**, are also readily generated by the methods above. Enolate **8a** is presumed to have the *E* geometry about the double bond, in analogy to the enolates of amides, and the enolate C-O bond is presumed to be *anti* to the carbonyl ligand (*vide infra*), as shown. Alkylation of **8a** with ethyl iodide at -78 °C affords **9a** and **9b** in a ratio of 98:2,<sup>9l,m</sup> though this ratio could be improved to as high as 200:1 by replacing the triphenylphosphine ligand with diethylamino-diphenylphosphine (Et<sub>2</sub>NPPH<sub>2</sub>)<sup>9m</sup> or using larger electrophiles, such as tosylates or Et<sub>2</sub>AlCl-complexed iodides.<sup>9b</sup>

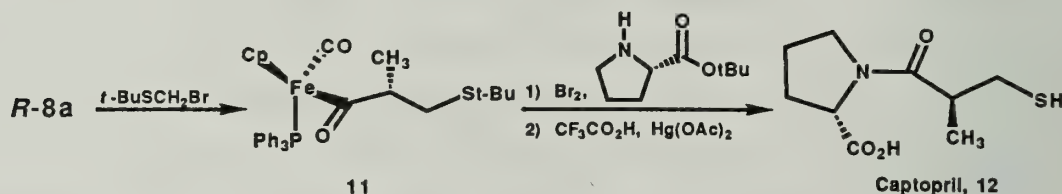


Enolate **8** also undergoes highly stereoselective reactions with aldehydes<sup>9f</sup> and ketones,<sup>9e</sup> but again a counterion other than lithium is required. Reaction of **8b** with aldehydes afforded 3 of the 4 possible diastereomers, the major adduct **10a** being formed in ratios (**10a**: all other isomers) of 7:1 to

100:1.<sup>9f</sup> Conversely, reaction of **8c** afforded **10b** as the major adduct in ratios (**10b**: all other isomers) of 7:1 to 25:1.<sup>9f</sup> Enolate **8c** also reacted diastereoselectively with symmetrical ketones in moderate to high yields.<sup>9e</sup>

The above methodology has been used in the synthesis of (-)-Captopril,<sup>9a</sup> a drug used in the treatment of hypertension, as shown in Scheme VI. Alkylation of pure *R*-**8a** with bromomethyl *t*-butyl sulphide afforded **11** in 71% yield. Oxidative decomplexation in the presence of L-proline *t*-butyl ester followed by deprotection afforded Captopril, **12**, in 83% yield (59% overall from **8a**).

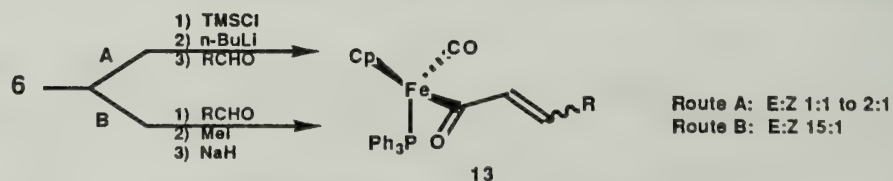
Scheme VI



#### REACTIVITY OF $\alpha,\beta$ -UNSATURATED IRON ACYL COMPOUNDS

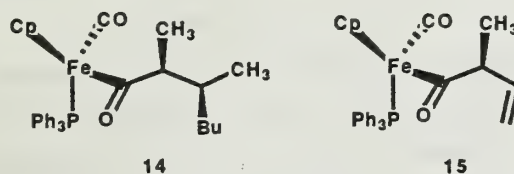
A great deal of effort has gone into studying the synthesis<sup>10a,b,g,h;13a,b,c</sup> and reactivity<sup>10c,d,e,f,i;13a,b</sup> of  $\alpha,\beta$ -unsaturated chiral iron acyl compounds, **13**. These compounds are readily available from a variety of routes (Scheme VII). The *Z*-olefin is most readily obtained as the minor isomer in the reaction of **6** with  $\text{TMSCl}$ , followed by deprotonation with *n*-BuLi and condensation with aldehydes.<sup>10h</sup> The *E*-isomer can be selectively formed by the treatment of **6** with an aldehyde followed by O-methylation with methyl iodide (MeI) and elimination of methoxide with sodium hydride (NaH),<sup>10g,h</sup> affording **13** in 90-95% yield as a 15:1 *E*:*Z* mixture. Note that the initial aldol condensation under these conditions shows little selectivity (*vide supra*), but that both  $\beta$ -methoxy acyl diastereomers give the same *E*:*Z* mixture of **13**.<sup>10g,h</sup>

Scheme VII



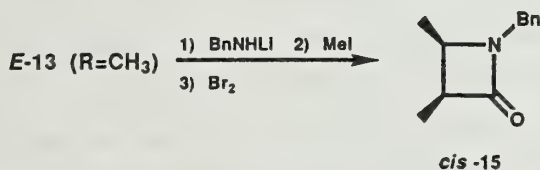
The stereoisomers *E*- and *Z*-**13** show quite different reactivities with alkyllithium reagents. Treatment of *E*-**13**,  $\text{R}=\text{CH}_3$ , with *n*-BuLi followed by MeI affords **14** as a result of initial conjugate addition and subsequent  $\alpha$ -alkylation of the enolate.<sup>10b,i</sup> Conversely, treatment of *Z*-**13**,  $\text{R}=\text{CH}_3$ , with *n*-

BuLi followed by MeI affords **15**, resulting from  $\gamma$ -deprotonation by *n*-BuLi and  $\alpha$ -alkylation by MeI.<sup>10b,f,i</sup> The  $\alpha$ -alkylation of various *Z*  $\alpha,\beta$ -unsaturated iron acyl compounds show similar results, and the diastereomer epimeric at the  $\alpha$ -carbon atom is seldom detected.<sup>10b,f</sup> Coordination of the alkyllithium to the electron-rich acyl oxygen prior to reaction is proposed to explain the differing reactivity;<sup>10b</sup> in *Z*-**13**, the  $\gamma$ -protons are proximate to the alkyllithium and are abstracted, while in *E*-**13** they are not and addition to the  $\beta$ -carbon atom is observed. This proposal is supported by the fact that in the presence of hexamethyl phosphoramide (HMPA), which presumably interferes with coordination to the carbonyl oxygen, LDA deprotonates *E*-**13**, while 1,4-addition is observed in the absence of HMPA.<sup>13a,b</sup>



$\alpha,\beta$ -Unsaturated acyl compounds **13** can also be used in the synthesis of  $\beta$ -lactams,<sup>10b,c,e;13a,b</sup> as shown in Scheme VIII. For example, treatment of *E*-**13** ( $R=CH_3$ ) with the lithium salt of benzylamine followed by trapping the enolate with methyl iodide and decomplexation with bromine affords the *cis*-dimethyl  $\beta$ -lactam **16**.<sup>10b</sup>

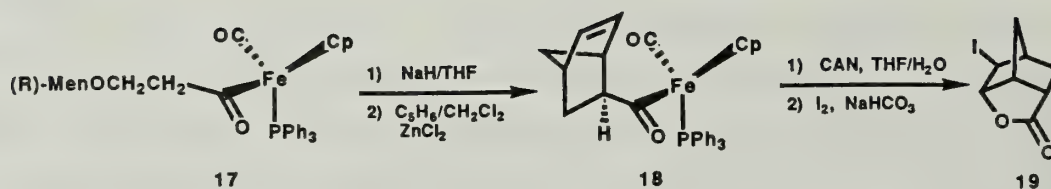
#### Scheme VIII



The use of chiral iron acyl compounds in asymmetric Diels-Alder reactions has just recently begun to be explored.<sup>10a,d</sup> Treatment of **6** with chloromethyl (*R*)-menthyl ether affords **17**, which can be resolved into the (*R,R*) and (*S,R*) diastereomers. Treatment of pure (*S,R*)-**17** (shown) with sodium hydride in THF results in the elimination of menthol to afford the unsubstituted  $\alpha,\beta$ -unsaturated acyl compound, which reacts with cyclopentadiene under zinc chloride catalysis to afford **18** and two other isomers in a ratio (**18**:all other isomers) of 84:16 and in 76% yield from **17**. Conversion of **18** to the known iodolactone **19** is achieved as shown in Scheme IX to afford **19** in 63% yield and 95% e.e., thus confirming the structural assignment for **18**.<sup>10d</sup>



## Scheme IX



## THEORETICAL AND CONFORMATIONAL STUDIES

The remarkable stereocontrol observed in reactions of chiral iron acyl compounds **3** has stimulated many conformational and theoretical studies in the Davies group.<sup>11</sup> Of particular interest are Extended Huckel calculations done on models of the parent acyl complex **4**. These calculations<sup>11b</sup> suggest that the carbonyl C-O and acyl C-O bonds prefer to be *anti* to one another due to the stereoelectronic effect of one of the phenyl rings on phosphorus, whereas a second phenyl ring forces the acyl C-O to be virtually in the plane defined by OC-Fe-COR. Examination of X-ray crystal structures of various acyl complexes,<sup>8d,9m,11e</sup> for example, **5**,<sup>9m</sup> show that this is indeed the conformation in the solid state.

From these calculations and others on iron<sup>11a,d,f</sup> and rhenium<sup>11d</sup> alkyl compounds, Davies and Seeman<sup>11e</sup> have developed a model to explain the stereoselectivity of reactions occurring at organic ligands (R or COR) of **2** and **3**. For the acyl complexes **3**, the stereoelectronic effect of the triphenylphosphine ligand (*vide supra*) forces the enolates **6** and **8** to adopt the conformations shown: enolate C-O and carbonyl C-O bonds are *anti* to one another and the enolate is virtually in the plane defined by C-Fe-C. The large PPh<sub>3</sub> ligand effectively blocks one face of the enolate from approach by electrophiles and this, combined with the preferential formation of the *E* enolate for **8**, leads to the high stereoselectivities observed for reactions at the  $\alpha$ -carbon. High selectivities at the  $\beta$ -carbon atom, i.e., in reactions with aldehydes, are not as affected by the stereogenic iron center, and are only achieved by the use of modified enolates (e.g., **8b** or **8c**). The mechanism of asymmetric induction at the  $\beta$ -carbon by metal additives is a subject of some debate,<sup>13a</sup> and further mechanistic studies are required.

## CONCLUSION

Chiral iron acyl compounds are an interesting and valuable addition to a class of rare chiral auxiliaries in which chirality derives solely from a stereogenic metal atom. Reactions at the acyl ligand exhibit predictable and



high stereoselectivity, and both enantiomers of the parent acyl compound **4** are commercially available. The versatility of these reagents is amply demonstrated by the wide variety of reactions they undergo. A current challenge that must be met for widespread use in asymmetric synthesis is recovery of the iron auxiliary in high enantiomeric purity.

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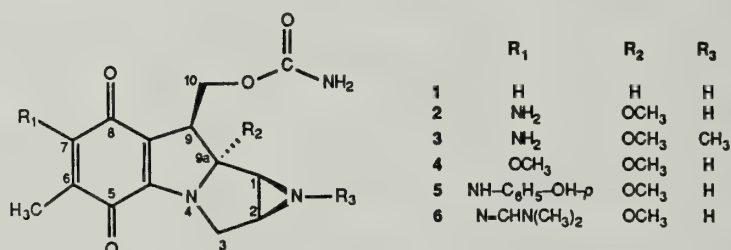
## MITOMYCINS: BIOREDUCTIVE ALKYLATING AGENTS

Reported by Nancy Fregeau

March 17, 1988

## INTRODUCTION

The mitomycins are a family of antitumor antibiotics which were first isolated from several *Streptomyces* species in the 1950's and 1960's.<sup>1</sup> They all possess a tetracyclic system which contains dehydroindoloquinone and aziridine units and has the trivial name mitosane (1). The mitomycins can be subdivided into two groups: those with a 7-amino substituent (i.e. mitomycin C, (2), and porfiromycin, (3)) and those with a 7-methoxy substituent (mitomycin A, (4)). Biosynthetic studies<sup>1a,b</sup> have led to a reevaluation of the absolute configuration.<sup>2</sup> Although many groups have attempted to synthesize these highly reactive molecules, only two have succeeded.<sup>3</sup>



Early on, the mitomycins showed promising activity against a wide array of tumors and microorganisms.<sup>1</sup> Mitomycin C (2) is the most effective of the naturally occurring compounds. Bristol Laboratories currently markets this drug, which received FDA approval for clinical use in 1974, under the trade name Mutamycin.<sup>1a</sup> It is used to treat stomach, pancreas and colon cancers, but this use is limited by its toxic side effects, which include leukopenia, thrombocytopenia, nausea, and vomiting.<sup>1a,b,4</sup> Porfiromycin (3) has also been investigated clinically because it has a lower toxicity level than 2, although it is less potent.<sup>5</sup> Only recently have any analogues been developed which have greater activity than 2. The C-7 analogs known as M-83 (5) and BMY-25282 (6) appear promising.<sup>6</sup>

## BASIC MECHANISM

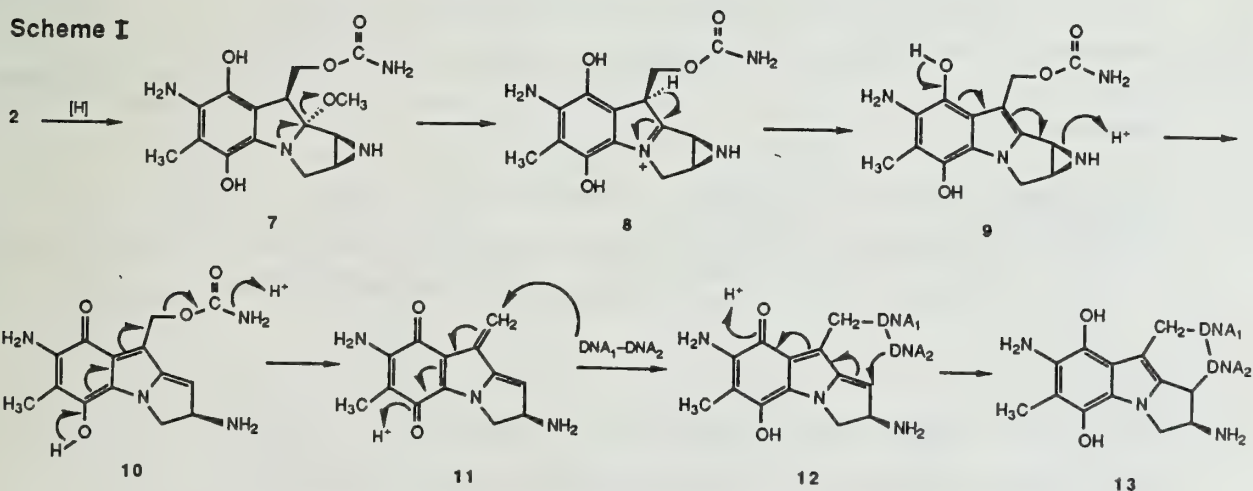
The clinical activity of the mitomycins has aroused a great deal of interest in their mode of action. They have long been known to inhibit DNA synthesis selectively.<sup>1c,7</sup> This activity is believed to be the result of cross-linked DNA, caused by one mitomycin molecule alkylating both strands, although monoalkylation may also have some effect.<sup>8</sup> One can easily imagine



a nucleophilic attack on the aziridine ring or  $S_N2$  displacement of the carbamate group by a base on the DNA chain. However, at neutral pH, the mitomycins are remarkably stable to such attack.<sup>1c,9</sup> The 9a-methoxyl group is also stable to elimination, even though it is part of a carbinolamine. The N-4 lone pair is conjugated with the quinone ring and thus is less able to assist in the elimination.

This stability of the mitomycins is contrary to their high activity *in vivo*. Schwartz et al. found that rat liver homogenates metabolized 2 much more rapidly under anaerobic than under aerobic conditions, leading them to propose that an enzymatic reduction activates the drug to alkylation.<sup>9</sup> Iyer and Szybalski determined more specifically that an NADPH-dependent enzyme is required to produce cross-linked DNA.<sup>10</sup> Further support for reduction as a means of activation *in vivo* is that the mitomycins are selectively toxic to hypoxic tumor cells.<sup>5,6a,11</sup> Under such low oxygen conditions, a highly reactive reduced intermediate could exist long enough to alkylate DNA. Also hypoxic cells have a higher concentration of NADPH.<sup>6a</sup>

Moore,<sup>12</sup> expanding on a mechanism suggested by Iyer and Szybalski,<sup>10</sup> has proposed that, after bio-reduction of the quinone 2 to the hydroquinone 7, methanol would be rapidly eliminated to give the aziridinomitosenone hydroquinone 9. The strained aziridine ring would then open, assisted by the hydroquinone. This product, 10, would eliminate the carbamate group, resulting in the highly reactive intermediate 11, which is alkylated at C-10 and C-1 by bases on opposite strands of DNA to give the cross-linked product 13 (Scheme I). Many variations can be imagined for this mechanism such as



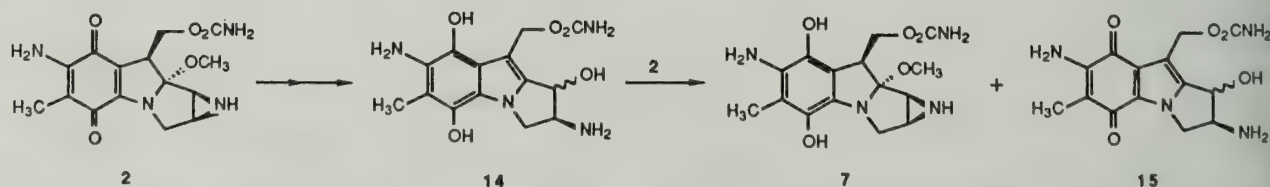
in a one-electron rather than a two-electron reduction and in the order of the alkylation steps. However, the basic ideas embodied by this mechanism—reductive activation, elimination of methanol followed by opening of the aziridine ring, and sites of alkylation—are generally accepted.

#### MODEL REDUCING SYSTEMS

Many attempts have been made to develop in vitro model systems to study the reductive activation of **2**. A number of chemical reducing agents have been used such as sodium dithionite,<sup>10</sup> sodium borohydride,<sup>10</sup> hydrogenation over platinum or palladium catalysts,<sup>9</sup> and hydrazine.<sup>13</sup> Several enzyme systems have been investigated including NADPH-cytochrome P-450 reductase,<sup>6a,14</sup> xanthine oxidase,<sup>6a,14</sup> DT-diaphorase,<sup>6a,10</sup> and NADPH: (acceptor) oxidoreductase.<sup>15</sup> Electrochemical reduction has also been studied.<sup>16</sup>

Few direct comparisons of these model reducing systems with actual in vivo activation have been reported. Catalytic hydrogenation with palladium on charcoal gave a mixture of alkylated products very similar to that produced in rat livers, but sodium dithionite and sodium borohydride produced different results.<sup>17</sup> In another study, catalytic hydrogenation and dithionite gave the same mono- and bisalkylation products with DNA, but in vastly different ratios. The bisadduct was also detected in vivo.<sup>18</sup> Peterson and Fisher<sup>15</sup> have shown that, even under strictly anaerobic conditions, the compounds produced by the reduction of **2** by Old Yellow enzyme and NADPH are oxidized back to the quinone and a nonstoichiometric amount of NADPH is used. Their results imply that an autocatalytic reaction occurs in which reductively activated **2** reacts to produce **14**. This mitosene then is oxidized to the quinone form (**15**) by unreduced **2**, causing a chain reaction (Scheme II).<sup>15</sup> Enzymatic reduction and catalytic hydrogenation

Scheme II

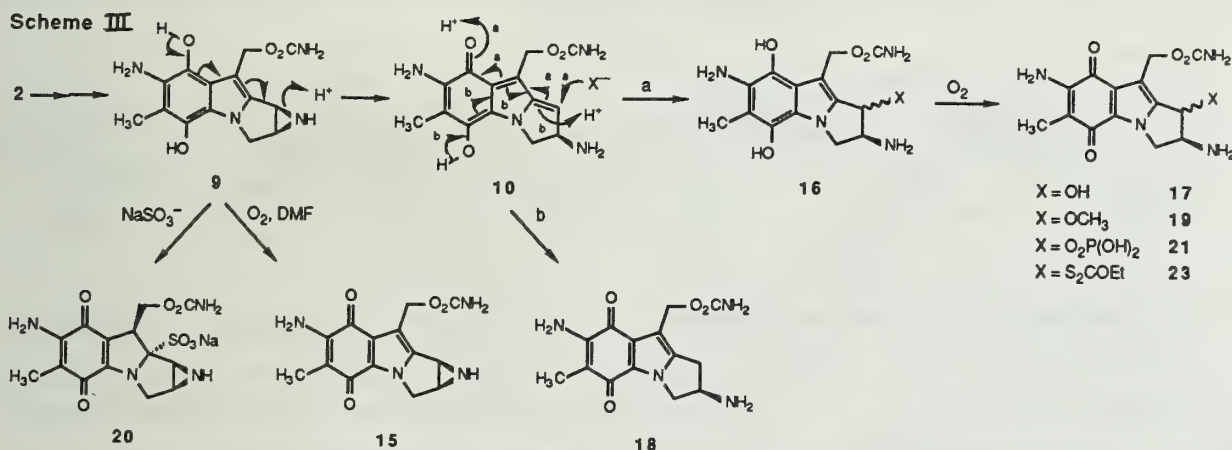


are slow processes which allow for autocatalysis. Reduction by dithionite is faster, causing **2** to be stoichiometrically reduced,<sup>18</sup> thus explaining the difference between the various activation methods. Enzyme inhibition studies suggest, at least in one tumor cell line, that xanthine oxidase and

DT-diaphorase do not participate in the *in vivo* reduction of mitomycins and that NADPH-cytochrome P-450 reductase contributes to the activation of the drug, but more than one enzyme must be involved.<sup>6a</sup>

#### EVIDENCE FOR ALKYLATION

Using these reducing systems, many workers have studied the decomposition products of mitomycins under reductive conditions. Methanol is rapidly eliminated upon reduction.<sup>10,19</sup> In DMF solutions, this produces an aziridinomitosenes (15).<sup>19</sup> Reduction by various enzyme systems results in nucleophilic attack on C-1 by water after methanol has been eliminated to give a mixture of the *cis*- and *trans*-hydroxymitosenes (17) (Scheme III). The

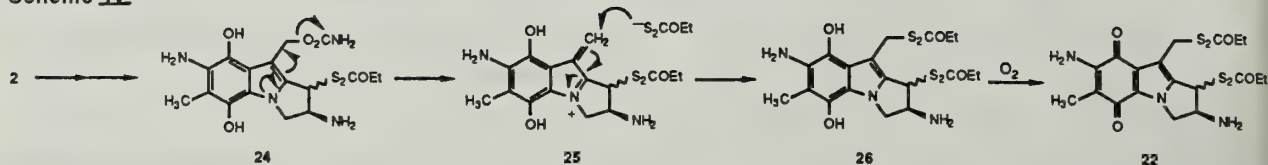


aziridine ring opens to form 10 prior to the nucleophilic attack by water, as 10 can itself act as a nucleophile to abstract a proton from the solvent, forming a mitosene (18).<sup>14a,15,20</sup> A one-electron electrochemical reduction of 2 in methanol produced the corresponding 1-methoxy derivative 19.<sup>16a</sup>

Various nucleophiles other than solvent have been used to trap the reactive reduced species. Hornemann et al. have reported that reduction of 2 by sodium dithionite or catalytic hydrogenation in an aqueous solution containing sodium sulfite gave sodium 7-aminomitosane-9a-sulfonate (20).<sup>21</sup> C-1 phosphate adducts (21) have been observed when 2 is reduced by catalytic hydrogenation, rat liver microsomes or various enzymes, but not by dithionite, in the presence of a phosphate buffer (Scheme III).<sup>14a,20a</sup> 1,10-Di(ethylxanthyl)-2,7-diaminodecarbamoylemitosene (22), resulting from dithionite reduction of 2 in the presence of potassium ethyl xanthate, was the first isolated 1,10-bisadduct (Scheme IV). The 1-ethylxanthyl derivative (23) was also produced, indicating that C-1 is alkylated first, in contrast to Moore's mechanism.<sup>22</sup>

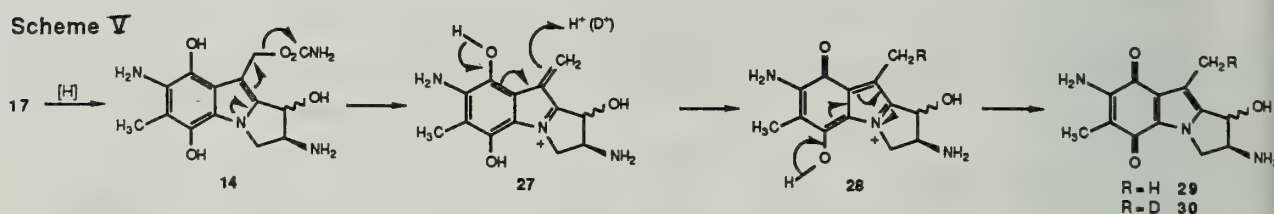


Scheme IV



Scheme I indicates that the carbamoyl group is lost before alkylation occurs at C-10. Alternatively, an  $S_N2$ -type reaction could occur. This latter proposal has been disproven.<sup>16a,b,23</sup> It was found that catalytic or electrochemical reduction of **17** produced the C-10 methyl derivative **29** (Scheme V). Deuterium incorporation at C-10 (**30**) was observed when the red-

Scheme V



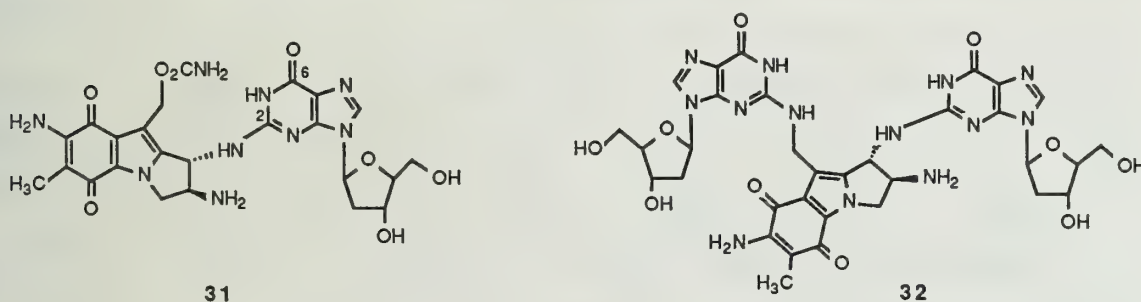
uction was run in deuteriomethanol, but not when the reduction was performed using deuterium, indicating that a proton was abstracted from the solvent.<sup>16a,23</sup>

Mitomycins have been known to cross-link DNA since 1963, but characterization of these adducts has proceeded slowly. Iyer and Szybalski<sup>10</sup>, by using cesium chloride density-gradient centrifugation, and Lown et al.<sup>24</sup>, by using ethidium fluorescence, have demonstrated that some DNA which had been treated with mitomycin under reducing conditions and then heat-denatured would spontaneously renature. The cross-linked DNA is stable even under conditions known to dissociate strongly bound noncovalent complexes of DNA, indicating that mitomycin is bound covalently.<sup>10,25</sup> By using [<sup>3</sup>H]-**2** and [<sup>14</sup>C]-**3**, Weissbach and Lisio showed that the total amount of mitomycin bound to DNA is 5-10 times larger than the amount of cross-linked DNA.<sup>1c,26</sup> However, more recent studies have suggested that the amount of dialkylated products could actually be much higher.<sup>14b</sup> The degree of cross-linking is higher under hypoxic conditions in vivo.<sup>11</sup>

Although Moore's mechanism details the reactive sites on the mitomycins, it makes no mention of what nucleophile on DNA is alkylated. The degree of cross-linking increases in proportion to the amount of guanosine (G) and cytidine (C) in the DNA.<sup>10</sup> Mitomycins alkylate poly-G<sup>27</sup> and poly-dG<sup>25</sup> to a



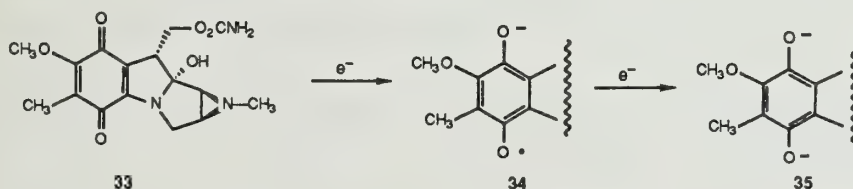
much greater extent than other homopolymers of nucleotides. Mitomycins do not bind well to mononucleotides,<sup>20a,28</sup> which suggests that some noncovalent interaction between the drug and DNA may be required prior to the actual alkylation.<sup>25</sup> This possibility has been substantiated by molecular mechanics simulation of noncovalent and mono- and cross-linked adducts of **2** with DNA.<sup>6b,18,29</sup> Enzymatic degradation of the product of **2** and d(GpC) or DNA led to the isolation of a mitomycin-deoxyguanosine adduct (**31**) in which a bond is formed between C-1 of **2** and N-2 of G.<sup>14c,30</sup> In 1987, Tomasz, Nakanishi, and coworkers first characterized spectroscopically an enzymatic degradation product of cross-linked DNA (**32**), prepared both in vitro and in vivo. This product had two deoxyguanosines bound (N-2) at C-1 and C-10.<sup>18</sup>



## TWO-ELECTRON VS. ONE-ELECTRON REDUCTION

Moore's mechanism assumes a two-electron reduction is required for activation. This hypothesis is based in part on an early electron spin resonance (ESR) study by Patrick et al. who found that the semiquinone of mitomycin B (**33**) is relatively stable in DMF, but that the corresponding hydroquinone under anaerobic conditions would eliminate methanol (Scheme VI).<sup>19</sup> Lown et al. have also concluded from their cyclic voltammetric

### Scheme VI



studies of **2** and **33** in aqueous solutions that the first step in the mechanism is a reversible two-electron, two-proton reduction. Their results indicate that the hydroquinone of **2** has a lifetime of 0.07 sec in water,

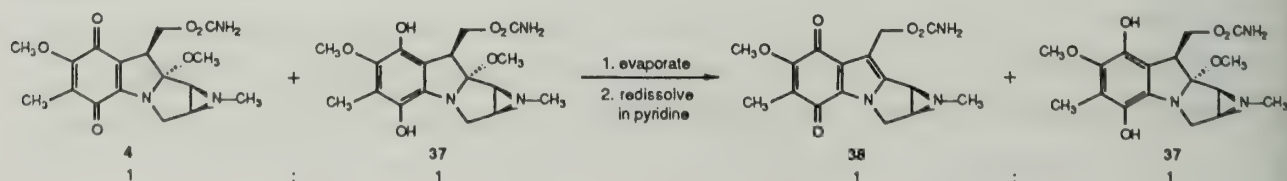
while the semiquinone has a lifetime of 10 sec. However these results do not eliminate the possibility of the semiquinone occurring *in vivo*.<sup>16c,d</sup>

This assumption of a requisite two-electron reduction has come under question. Recent work suggests only a one-electron transfer is necessary to activate **2**. The quinone anion radical, generated electrochemically under anaerobic conditions, is stable in aprotic solvents, as shown by ESR, but in protic solvents, ring-opened compounds such as **17** and **18** rapidly appear.<sup>16a,b</sup> The ratio of these products is similar to that produced by NADPH-cytochrome P-450 or xanthine oxidase which are known to favor single electron reduction.<sup>14a</sup> Although a one-electron transfer may result in monoalkylation, a second reduction may be required for bisadduct formation, as the lower potential electrochemical reduction caused no activation at C-10, but a two electron reduction gave 10 decarbamoyl products.<sup>14a,16b</sup> Whether the initial monoadduct of **2** and DNA can be reduced and subsequently form a cross-link<sup>14a,16b</sup> or whether a two-electron reduction is required prior to any alkylation steps to produce a cross-link<sup>14b</sup> is still unclear.

Tomasz et al. have compared the binding affinity of **2** when reduced (a) by an excess of dithionite added all at once and (b) by a stoichiometric amount added in five equal portions at five-minute intervals. The latter case, where a build up of semiquinone radicals (**36**) could occur, resulted in greatly increased binding to DNA. If a large excess of **2** was used, thus maximizing the concentration of **36**, even more binding to DNA was observed.<sup>25</sup>

Other support for a one-electron reduction comes from Danishefsky's work with "leucomitomycins" (mitomycin hydroquinones). Catalytic hydrogenation of **2** in pyridine under anaerobic conditions results in leucomitomycin C (**7**) which is stable for at least 24 hours.<sup>31</sup> He has also synthesized leucoaziridinomitosenes (cf. **9**).<sup>31a,32</sup> When a 1:1 mixture of **4** and the corresponding hydroquinone (**37**) was evaporated and redissolved in pyridine under anaerobic conditions, it gave a 1:1 mixture of **37** and the aziridinomitosene (**38**) (Scheme VII). This appears to be the result of disproportionation of the semiquinone.<sup>31a</sup>

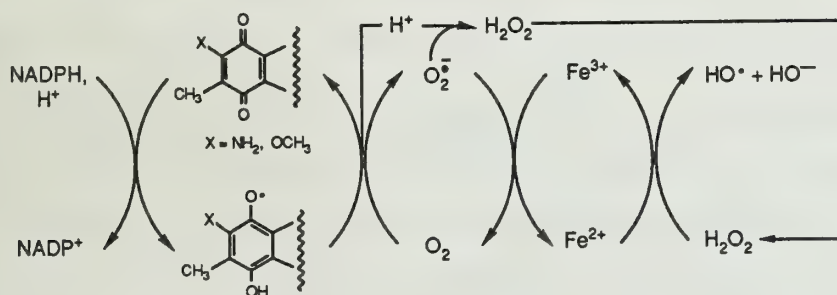
#### Scheme VII



## OTHER MECHANISMS

The reductive mechanism and its variations discussed so far may not be the only mode of action involved in the antitumor activity of these drugs. Under acidic conditions, a similar sequence of events takes place.<sup>8,24,33</sup> This mode of action may be important in gastric and solid tumors, which are known to have lower pH levels,<sup>33a</sup> and may also explain some of the drug's toxicity.<sup>34</sup> Also, in oxygenated cells, the semiquinone radical produced may be reoxidized by  $O_2$  producing superoxide radicals ( $O_2^{\cdot-}$ ) which form hydroxide radicals ( $HO^{\cdot}$ ) which cause scission of the DNA chain (Scheme VIII). This reduction-reoxidation process can occur repeatedly. Decomposition and even alkylation products may be involved.<sup>6a,c,18,24</sup>

Scheme VIII



## CONCLUSION

While the mode of action of this family of drugs has been studied for more than 25 years, the subject still is of interest. The mechanism is fairly well understood, but some questions remain. Knowledge of the mode of action may help in designing more potent analogues. Moore and others are currently trying to develop other types of bioreductive alkylating agents.<sup>12,35</sup> These agents may be important because they can selectively attack hypoxic tumor cells, which, in general, are resistant to radiation and some other forms of chemotherapy.<sup>6a</sup>

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# AN EXAMINATION OF REMOTE ASYMMETRIC INDUCTION IN MEDIO- AND MACROCYCLIC COMPOUNDS THROUGH CONFORMATIONAL ANALYSIS

Reported by Ellen M. Radzilowski

March 21, 1988

## INTRODUCTION

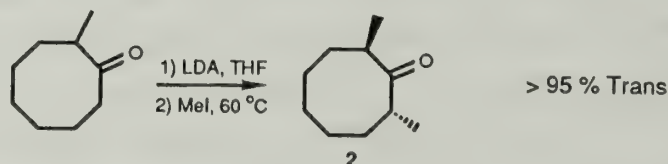
The total synthesis of macrocyclic compounds with multiple asymmetric centers, substituents and functional groups has been the goal of synthetic organic chemists for many years. These compounds are interesting because of their importance as antibiotics and other natural products. There are two distinct problems associated with the synthesis of macrocycles: controlling the stereochemistry of the carbon skeleton and closing the ring.<sup>1</sup>

The control of absolute stereochemistry is often accomplished by the elaboration of acyclic precursors which possess centers of absolute stereochemistry.<sup>2</sup> Vicinal asymmetric centers can be controlled in these precursors or in the macrocycle itself by the use of enantiomerically pure reagents, various chiral auxiliaries,<sup>3</sup> or reagents that react stereoselectively due to chiral centers<sup>4</sup> or functional groups<sup>5</sup> on the substrate. These fragments containing centers of absolute stereochemistry must then be connected and the ring closed while maintaining the stereochemical integrity of all the centers. It is the control of the remote asymmetric centers, those separated by more than 2 carbons, that present a problem upon coupling of the precursors and ring closure.

## MACROCYCLES AS A MEDIUM FOR ASYMMETRIC INDUCTION

In recent years, it has been reported that relative stereochemical relationships can be induced in macrocycles as a consequence of conformational properties.<sup>6</sup> A single stereogenic center in the substrate has been shown to control effectively, even if it is far removed from the reaction site. An example of asymmetric induction in a macrocyclic compound is the kinetic alkylation of 2-methylcyclooctanone shown in Scheme I.<sup>6</sup>

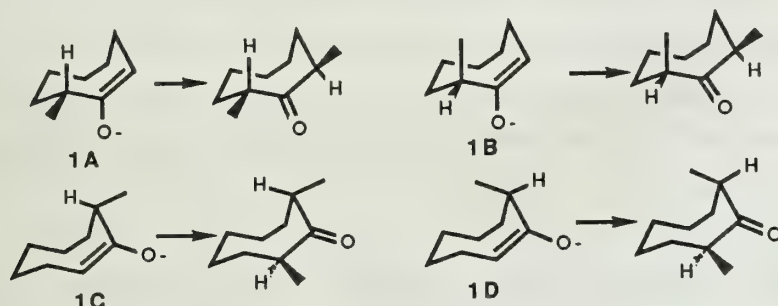
Scheme I



Several points should be addressed at this time. First, previous studies have indicated an early reactant-like transition state for kinetic enolate

methylations.<sup>7</sup> Therefore, to explain the selectivity of the above reaction, one can examine the enolate conformations. If one assumes a favored boat-chair (BC) conformation, there are four possible enolate and product geometries, which are shown in Scheme II. Alkylation would favor reaction by the lowest energy enolate conformation, 1A.<sup>6</sup>

Scheme II



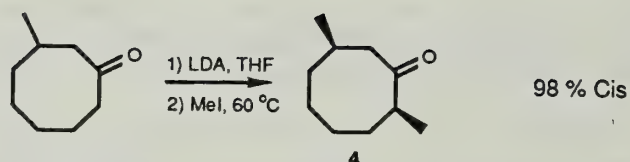
Second, the methyl substituent prefers the pseudoequatorial position as in cyclohexane so 1B and 1D are less favorable for the transition state. In both 1C and 1D, severe transannular nonbonded repulsions occur between the hydrogens on carbons 4 and 8 as alkylation proceeds which again are not favored in the transition state. Finally, the enolate moiety will lie perpendicular to the plane of the ring so as to minimize transannular interactions. Therefore, in the transition state, the reagent will approach the unsaturated center from the periphery of the open face to avoid the steric bulk of the ring.<sup>6</sup>

As indicated above and in the reactions that follow,<sup>8</sup> it is assumed that the reactions are kinetically controlled and that the transition state will adopt the lowest energy conformations which are closely related to the ground state structures. One can therefore expect high asymmetric induction considering conformational biasing by ring substituents in addition to the preference for least hindered peripheral attack. The approach of constructing a ring to provide stereocontrol in the synthesis of complex molecules will be shown by an examination of reactions on simple medio- and macrocycles followed by its successful use in specific syntheses.

#### DISTANCE BETWEEN REMOTE CENTERS

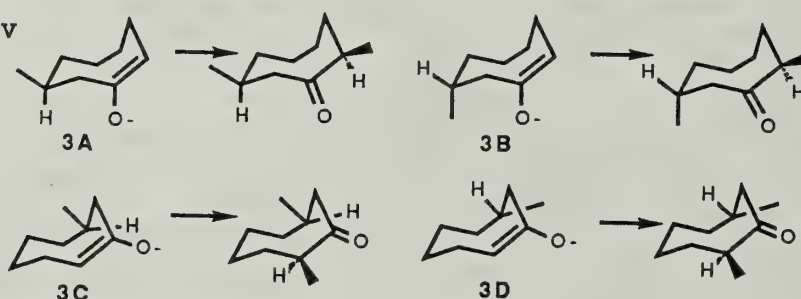
One question to address is the distance through which a substituent can influence the stereocontrol of a given reaction. In comparison to the example in Scheme I, which exemplifies 1,3 asymmetric induction, the kinetic enolate methylation of 3-methylcyclooctanone illustrates an example of 1,4 asymmetric induction as shown in Scheme III. Here, the *cis* isomer is

Scheme III



predominantly produced.<sup>6</sup> This product can be explained by again assuming the transition state resembles the most stable enolate geometry shown in Scheme IV. Considering the steric factors and conformational preferences described for 2-methylcyclooctanone, the favored pathway would have a transition state structure resembling 3A, with peripheral attack to provide the *cis* isomer.<sup>6</sup>

Scheme IV



Kinetic enolate methylations of methyl-substituted 10-membered lactones in Table I illustrate that selectivity falls as the distance between centers becomes too great.<sup>6</sup>

Table I      Kinetic Enolate Methylation of 10-membered Lactones		
Reactant	Product	Cis/Trans Ratio
		> 99 : 1
		86 : 14
		1 : 1

The major isomer observed can be rationalized by assuming the transition state geometry of the enolate resembles a BCB conformation. The 9-methylated enolate, obtained from 5, prefers an axial substitution since the 1,3 methyl-hydrogen transannular interactions are less severe than the 1,3



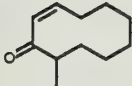
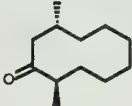
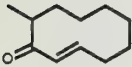
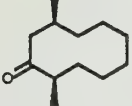


methyl-alkoxide transannular interactions to provide 1,4 asymmetric induction. To see 1,5 asymmetric induction, one can consider the 8-methylated enolate, obtained from 6, in which the normal preference for equatorial substitution is observed. The 7-methylated enolate, obtained from 7, offers no control because there are gauche-butane interactions for either geometry in this corner position.<sup>6</sup> Thus, the distance from the reaction site becomes a factor to asymmetric induction when the substituent has no preference for a conformation due to its location in the ring.

#### STEREOELECTRONIC EFFECTS ON CONFORMATIONAL PREFERENCES

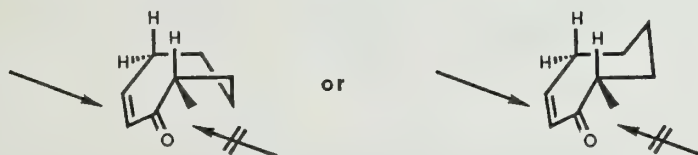
Stable conformations in simple medio- or macrocycles are those that minimize torsional strain and transannular nonbonded interactions. When additional functional groups are introduced, stereoelectronic effects need to be considered. For example, the lithium dimethyl cuprate addition to 8-methylcyclooct-2-en-1-one results in a single (*trans*) product as shown in the first row of Table II.

Table II Lithium Dimethyl Cuprate Additions to 8- and 10-membered Enones

Reactant	Product	Trans / Cis Ratio
		> 99 : 1
		94 : 6
		6 : 94

This result can best be interpreted as arising from a transition state that resembles one of the low energy conformations of the enone shown in Scheme V which provide a planar  $\pi$  system. Alternatively, a typical BC

Scheme V

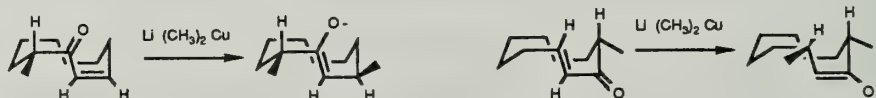


conformation would force the  $\pi$  system out of planarity, increasing the strain energy. The dimethyl cuprate could attack the open face of the enone

as shown, while the other face is hindered by the methylene groups present in the ring.

The dimethyl cuprate addition to *cis* and *trans* enones in 10-membered rings (Table II) further illustrate stereoelectronic effects on preferred conformations. The transition state geometry of the reaction may resemble the low energy BCB conformation of the enone shown in Scheme VI where the pi system remains planar and the methyl group shows pseudoequatorial preference. Attack by the nucleophile could occur from the less hindered peripheral face to provide the isomer observed.

Scheme IV



#### LOCAL CONFORMER CONTROL

Vedejs and coworkers<sup>9</sup> emphasize local conformer control in which the ring segment that contains the active site, a double bond, will adopt only certain geometries which are conducive to remote stereocontrol. Table III illustrates the most interesting results involving 12-membered olefins.<sup>9</sup>

Table III Epoxidation and Osmylation of E - and Z - olefins in 12- membered Rings

Reactant Conformation	Product Conformation	R Group	Product Group	Trans / Cis Ratio
<u>E - olefins</u>				
		H	X, Y = O	1 : 6
	1,3 Cis		X = Y = OH	1 : 1.9*
		CH <sub>3</sub>	X, Y = O	1 : 20
	1,3 Trans		X = Y = OH	1 : 20
<u>Z - olefins</u>				
		H	X, Y = O	> 20 : 1
	1,3 Trans		X = Y = OH	> 20 : 1
		CH <sub>3</sub>	X, Y = O	> 20 : 1
	1,3 Cis		X = Y = OH	> 20 : 1

\* Predominant isomer unknown

Results of epoxidations and osmylations show that the assumed geometry of the transition state correlates well with the model of peripheral attack.<sup>1f,10</sup> Epoxidations of medium ring alkenes with *meta*-chloroperbenzoic acid occur with selectivity as local conformer predicts, but the more sterically hindered osmium tetroxide reagent may result in less selectivity.<sup>9</sup> Other methods of stereoselective epoxidation require an adjacent hydroxyl group.<sup>5</sup>

Selectivity for epoxidation in the *E*-olefin series is good where the transition state structure is assumed to resemble a crown-like geometry about the double bond and substituents occupy a pseudoequatorial position. In osmylations, the selectivity may drop due to steric hindrance of the pseudoequatorial methyl group toward the bulky OsO<sub>4</sub>-L<sub>2</sub> reagent. If the ring adopts a conformation where the methyl is pseudoaxial, the osmium complex could attack preferentially from the periphery. The *Z*-olefins, however, result in high selectivity and the transition state appears to resemble the expected conformations.<sup>9</sup>

Vedejs<sup>11</sup> has reported the local conformer effects on 12-membered lactones possessing an endocyclic double bond with an allylic methyl group and an allylic lactone. The results for *E*-olefinic lactones are illustrated in Table IV.

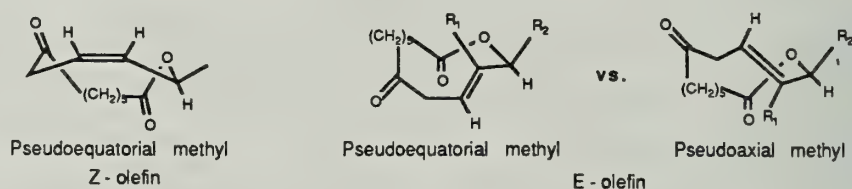
Table IV Epoxidations and Osmylations of 12- membered olefinic lactones					
Reactant	Product	R Groups		Trans / Cis	Ratio
<u>E - olefins</u>					
		R <sub>1</sub> = H	R <sub>2</sub> = CH <sub>3</sub>	0 : 100	
	1,3 cis	R <sub>1</sub> = CH <sub>3</sub>	R <sub>2</sub> = CH <sub>2</sub> CH <sub>3</sub>	1 : 1.5	
	1,3 trans				
		R <sub>1</sub> = H	R <sub>2</sub> = CH <sub>3</sub>	3 : 1	
	1,3 cis	R <sub>1</sub> = CH <sub>3</sub>	R <sub>2</sub> = CH <sub>2</sub> CH <sub>3</sub>	1.5 : 1	
	1,3 trans				

The *E*-olefins react in epoxidations from a typical crown-like geometry about the olefin as well as keeping the alkyl substituted lactone in a transoid geometry as shown in Scheme VII. This favored conformation with an equatorial methyl group produces a single (*cis*) isomer in the disubstituted

olefin, but only a 1.5:1 *cis*/*trans* ratio in the trisubstituted olefin. However, osmylation results in the opposite isomer which can be explained by assuming a crown-like environment with an axial methyl group as shown in Scheme VII. Thus, the osmate ester can be formed from peripheral attack avoiding both the steric bulk of the ring and ligand-methyl interactions.<sup>11</sup>

The product ratios for the disubstituted *Z*-olefins are more predictable for both epoxidations and osmylations. The conformer that can provide these ratios is the same as shown earlier in Table III with carbocyclic *Z*-olefins. However, selectivity has dropped to a 3:1 *trans*/*cis* ratio from 20:1 possibly because of competing transition states where there are conflicting preferences for the *Z*-alkene and transoid lactone. Scheme VII shows the conformer which the transition state may resemble for the *Z*-olefin.<sup>11</sup>

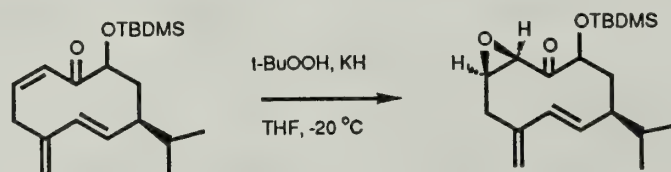
Scheme VII



#### EPOXIDATIONS IN MEDIOCYCLIC NATURAL PRODUCTS

The stereocontrolled synthesis of the American cockroach sex pheromone, periplanone-B, has been reported. The 10-membered ring requires a stereoselective epoxidation as the key step. As shown in Scheme VIII, Still has prepared the epoxy ketone as a 4:1 mixture of isomers.<sup>12</sup>

Scheme VIII



The desired epoxide could be obtained from a BCC conformation in which the conjugated diene adopts an *s-trans* conformation which would be favored over an *s-cis* conformation.



Schreiber and Santini<sup>13</sup> have also obtained a 4:1 mixture of the desired isomer. However, Takahashi<sup>14</sup> has improved upon the synthesis by replacing the exocyclic double bond with a *tert*-butyl-diphenylsilyloxymethyl

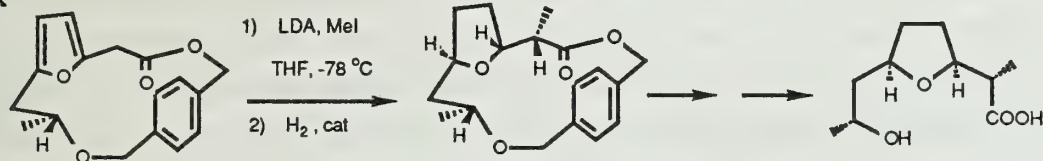


substituent to obtain only the *cis* isomer. It can be inferred that the BCC conformation that allowed an *s-trans* conformation is more favored since the silyloxy group can assume a pseudoequatorial position.

#### RING FORMATION TO CONTROL STEREOCHEMISTRY IN ACYCLIC MOLECULES

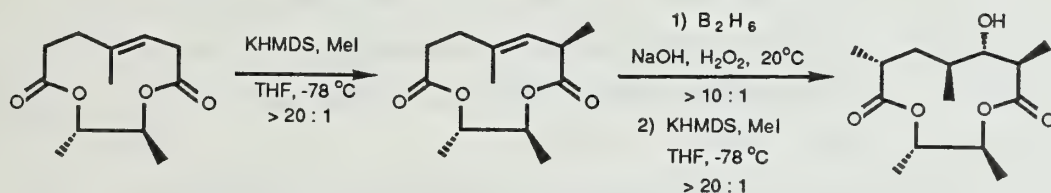
Conformational bias may be used for remote asymmetric induction in an acyclic molecule by inserting an auxiliary spacer between the ends of the acyclic compound to generate a ring. The synthesis of nonactic acid by this method begins with the incorporation of a xylene spacer and one asymmetric center to provide stereocontrol for kinetic enolate alkylation.<sup>6</sup> The furan ring and the xylene group lies perpendicular to the plane of the macrocycle. Therefore, the faces of the furan ring and the adjacent methylene group are easily distinguished as illustrated in Scheme IX. Reduction of the furan ring should generate the desired isomer, but final results were not reported.<sup>15</sup> Many alternate syntheses<sup>16</sup> have been reported for nonactic acid, but these are not stereocontrolled with the exception of Bartlett's total synthesis.<sup>17</sup>

Scheme IX



The C-3 to C-9 segment of lysocellin can be synthesized by first joining the ends with a spacer containing two asymmetric centers from (*S,S*)-2,3-butanediol to form a 11-membered dilactone containing a double bond. These two centers along with conformational requirements of the endocyclic bond appear to provide enough control to generate the remaining asymmetric centers with desired relative stereochemistry as shown in Scheme X. The spacer can then be removed to afford the acyclic molecule.<sup>15</sup>

Scheme X



#### CONCLUSION

In conclusion, conformational properties of medio- and macrocyclic molecules can have a profound effect on the stereochemical course of reactions. The macrocyclic approach to synthesizing molecular assemblies

with an array of remote asymmetric centers is a viable technique because of the high stereoselection of reagents for least hindered peripheral attack. By using the macrocycle itself as a medium for stereochemical control, the problem of controlling remote centers may be solved. A method for synthesizing acyclic molecules may be to construct a macrocycle and allow the conformational bias to induce remote stereocontrol.

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# **SAMARIUM DIIODIDE: A VERSATILE SINGLE ELECTRON TRANSFER REAGENT FOR ORGANIC SYNTHESIS**

Reported by Donald J. Gallagher

March 24, 1988

## **INTRODUCTION**

In the early 1980's Kagan reported the easy preparation and some reactions of samarium diiodide ( $\text{SmI}_2$ ).<sup>1</sup> The reagent acts primarily as a single electron transfer reagent and its usefulness stems from its solubility in tetrahydrofuran (THF) and its large reduction potential,  $-1.55$  V, which is among the highest known for an organic solvent-soluble reagent. Although it is a powerful single electron transfer reagent, samarium diiodide often shows remarkable selectivity and is able to carry out a wide range of reactions including reductions, carbonyl additions, and cyclopropanations.

## **PREPARATION OF THE REAGENT**

Samarium diiodide is usually prepared by the reaction of excess samarium and diiodoethane in dry THF at room temperature. Reaction is complete in about an hour to yield a dark blue-green solution of samarium diiodide. Various titrations indicate the yield is quantitative.<sup>1a,b</sup> Samarium diiodide has also been prepared by the reaction of samarium and diiodomethane,<sup>2</sup> as well as by the reaction of the metal and  $\text{I}_2$ . This last procedure suffers from the necessity of refluxing overnight.<sup>3</sup>

Usually solutions of samarium diiodide are used immediately, although the reagent can be stored for a few days under an inert atmosphere. When a stoichiometric amount of the reagent is used, completion of a reaction is conveniently indicated by disappearance of the blue color.

## **REDUCTION REACTIONS**

### **Reduction of Carbonyl Groups**

Samarium diiodide has been shown to be a versatile and selective reducing agent. Ketones and aldehydes are reduced to alcohols in one day at room temperature in good yields with 2 equivalents of the reagent and 2 equivalents of a proton source, usually methanol (Table I).<sup>1a</sup> Aldehydes are reduced much easier than ketones, and in competition experiments between ketones and aldehydes the aldehyde is reduced almost exclusively (90-96%). Esters and acids are unreactive towards samarium diiodide.



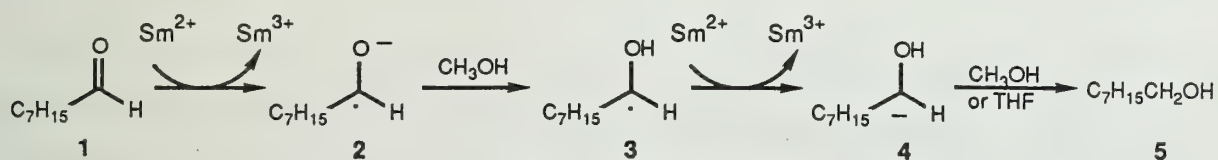
Table I: Reduction of Carbonyl Groups by  $\text{SmI}_2$ 

Reactants	Products	% Yield <sup>a</sup>
2-octanone	2-octanol	64 <sup>b</sup>
acetophenone	1-phenylethanol	80
octanal	1-octanol	99
octanal + 2-octanone (1:1)	1-octanol + 2-octanol	96:4
octanal + 4-t-butylcyclohexanone (1:1)	1-octanol + 4 t-butylcyclohexanol	90:10
octanoic acid	no reaction	-
methyl octanoate	no reaction	-

a) G.C. yields determined with an internal standard b.) 2 mmol  $\text{H}_2\text{O}$  used instead of methanol.

The mechanism of the reaction, shown for octanal (**1**) in Scheme I, is believed to involve initial electron transfer to the carbonyl group to produce the radical anion **2**, which then abstracts a proton from methanol to give the radical **3**. Another electron transfer from samarium diiodide to the radical produces the anion **4**, which abstracts another proton to form 1-octanol (**5**).

Scheme I



### Reduction of Double Bonds and Related Systems

Kagan also reported that cinnamic acid and ethyl cinnamate were reduced by samarium diiodide in 98% yield (GC) to the saturated acid and ester.<sup>1a</sup> Isolated double bonds, as well as cinnamyl alcohol, were found to be inert. Since no other systems were investigated, the scope of this reaction is not known. The reaction is believed to proceed via electron transfer to the double bond to form the radical anion, which is quenched by methanol, followed by sequential electron transfer and proton quench to the saturated compound.

Molander expanded this methodology to stereospecifically reduce vinyl epoxides to allylic alcohols.<sup>5</sup> The reduction of unsaturated epoxyesters is shown in Table II. When there was a choice of double bond stereochemistry, the (*E*)-allylic alcohol was usually produced exclusively. As shown in the last entry, reduction of a chiral epoxide (95% ee) provided the chiral allylic alcohol in 84% yield and 95% ee.

Table II: Reduction of Vinyl Epoxyesters with  $\text{SmI}_2$ 

Epoxide	Product	% Yield <sup>a</sup>
		77
		75
		81
		84 <sup>b</sup>

a) Isolated Yields b) 95% ee. (Starting material 95% ee.)

In addition to unsaturated esters, reactions of other vinylic epoxides were also studied. These reactions proceeded readily using alkenes with electron withdrawing substituents. Some substituents that provided good yields of allylic alcohols were  $-\text{COMe}$ ,  $-\text{CN}$ ,  $\text{COSEt}$ ,  $\text{SO}_2\text{Ph}$ , and  $\text{PO}(\text{OEt})_2$ .

The reduction of vinyl epoxides to (*E*)-allylic alcohols provides the same regioselectivity as the calcium-liquid ammonia system,<sup>6a</sup> which has been used only to reduce unfunctionalized alkenes. An advantage of samarium diiodide is that liquid ammonia is not needed; the reaction occurs under essentially neutral conditions. Reduction by samarium diiodide is complementary to the reduction of vinyl epoxides by diborane-THF and related reagents,<sup>6b</sup> which give the (*Z*)-allylic alcohols.

Molander has shown that samarium diiodide reduces a wide range of  $\alpha$ -heterosubstituted ketones to the corresponding ketones in good yield (Table III).<sup>7</sup> This reaction proceeds under mild, neutral conditions (2 equiv.  $\text{SmI}_2$ , THF- MeOH,  $-78^\circ$ ) unlike many commonly used methods, which often involve acidic conditions.<sup>8</sup> The selectivity of the reaction is quite good. Primary iodides are inert when only 2 equivalents of samarium diiodide are used.

Only reduction at the  $\alpha$ -position occurs so that in a competition between an acetoxy ketone and cyclohexanone no reduction of cyclohexanone was observed.

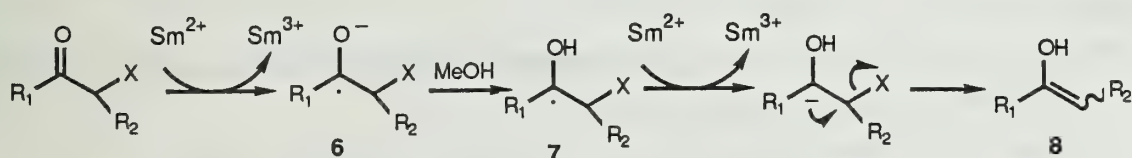
Table III: Reduction of Heteroatom Substituted Ketones with  $\text{SmI}_2$

$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{CH}(\text{R}')-\text{X} \end{array}$		$\xrightarrow[\text{THF, CH}_3\text{OH}]{2 \text{ SmI}_2, -78^\circ}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{CH}_2-\text{R}' \end{array}$
R	R'	X	% Yield <sup>a</sup>
$\text{C}_5\text{H}_{11}$	$\text{C}_5\text{H}_{11}$	OAc	75 <sup>b</sup>
$\text{C}_5\text{H}_{11}$	$\text{C}_5\text{H}_{11}$	OSiMe <sub>3</sub>	98
$\text{C}_5\text{H}_{11}$	$\text{C}_5\text{H}_{11}$	OTs	94
$\text{C}_5\text{H}_{11}$	$\text{C}_5\text{H}_{11}$	OH	29
$\text{C}_5\text{H}_{11}$	$\text{C}_5\text{H}_{11}$	Cl	100
$\text{C}_5\text{H}_{11}$	$\text{C}_5\text{H}_{11}$	SPh	76
$\text{C}_5\text{H}_{11}$	$\text{C}_5\text{H}_{11}$	SOPh	64
$\text{C}_5\text{H}_{11}$	$\text{C}_5\text{H}_{11}$	SO <sub>2</sub> Ph	88
$\text{C}_5\text{H}_{11}$	$\text{C}_5\text{H}_{11}$	HgCl	94
Ph	(CH <sub>2</sub> ) <sub>3</sub> I	OAc	87 <sup>b</sup>

a) G.C. Yields b) Isolated Yields

The proposed reaction mechanism is shown in Scheme II. Initial electron transfer from samarium diiodide to the ketone produces the ketyl radical anion **6**, which is protonated by methanol to give the radical **7**, followed by another electron transfer from samarium diiodide and beta elimination to yield the enol **8**. Ketyl radical formation is believed to occur in all reactions of samarium diiodide with ketones and aldehydes.

Scheme II



Molander also applied the same type of reaction in the reduction of  $\alpha,\beta$ -epoxyketones to  $\beta$ -hydroxyketones.<sup>9</sup> As shown in Table IV, yields of the aldol-type products are usually very good. In cases where the starting epoxide was chiral, retention of stereochemistry at the  $\beta$ -position was observed. These reactions were carried out preferentially in THF at  $-90^\circ$  with 1 equivalent epoxyketone, 2 equivalents samarium diiodide, and excess methanol. Reaction was complete in 5 min. The mechanism of the reaction is

thought to be analogous to that proposed for the reduction of  $\alpha$ -hetero ketones; elimination opens the epoxide stereospecifically and yields the aldol product. These results, along with those from the reduction of vinyl epoxides, illustrate the potential usefulness of samarium diiodide in asymmetric synthesis involving epoxides.

**Table IV: Reduction of Epoxyketones with  $\text{SmI}_2$**

Starting Material	Product	% Yield <sup>a</sup>
		97
		81
		79 <sup>b</sup>
		94 <sup>c</sup>

a) Isolated Yields b) Only one diastereomer produced. c) 90% ee. (S.M. 95% ee.)

Samarium diiodide has also been used as a reducing agent for isoxazoles<sup>10</sup> and as a deprotecting agent for chloroethyl carbamates.<sup>11</sup> Kagan has shown that it could be used to reduce halides and tosylates,<sup>1a</sup> but the conditions are rather harsh (THF, reflux) and it is not the reagent of choice for these reactions.

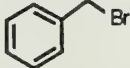



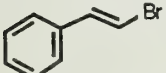
#### ADDITIONS TO KETONES AND ALDEHYDES MEDIATED BY SAMARIUM DIIODIDE

##### Intermolecular Reactions

Kagan found that alkyl, allyl, and benzyl halides add to ketones in the presence of samarium diiodide in a reaction formally analogous to Grignard reactions.<sup>1a</sup> In general, benzylic and allylic halides reacted much faster than alkyl iodides, which provided better yields of products than alkyl bromides. Phenyl and vinyl halides, as well as alkyl chlorides, did not react. Yields were usually improved by excess samarium diiodide and halide. Some of these reactions, which were carried out with 2 equivalents of samarium diiodide, 1 equivalent of halide, and 1 equivalent of ketone, are shown in Table V.



Table V:  $\text{SmI}_2$  Mediated Alkylations of Ketones.

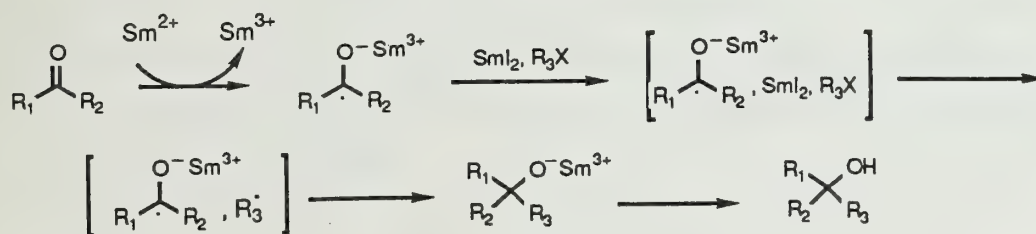
$\text{RX} + n\text{-C}_6\text{H}_{13}\text{C(=O)CH}_3 \xrightarrow{2 \text{ SmI}_2, \text{ THF}}$ $\begin{matrix} \text{H}_3\text{C} & \text{OH} \\ & \diagup \quad \diagdown \\ & \text{R} \end{matrix}$		
RX	Time, Temp.	% Yield <sup>a</sup>
	25 min, RT	69
	15 min, RT	71
	3 hr, RT	73
	2 days, RT	64
	2 days, 65°	N.R.

a) G.C. yields determined with an internal standard.

Addition of alkyl halides to aldehydes did not proceed in good yield because of competing pinacol formation,<sup>12</sup> while addition of benzylic halides and allylic halides has been reported to proceed readily.<sup>13</sup>

The mechanism is quite different from that of a Grignard reaction. As shown in Scheme III, the reaction occurs through formation of the ketyl, followed by formation of a radical ( $\text{R}_3\cdot$ ), formed from the reaction of a second equivalent of samarium diiodide with the halide. There is considerable evidence that the ketyl radical anion plays an important complexing role in the formation of this radical because no self-coupling is observed, while in the absence of a ketone such coupling occurs readily.<sup>1c</sup> Coupling between the radical and the ketyl occurs to form the samarium alkoxide, which on workup gives the alcohol.

Scheme III

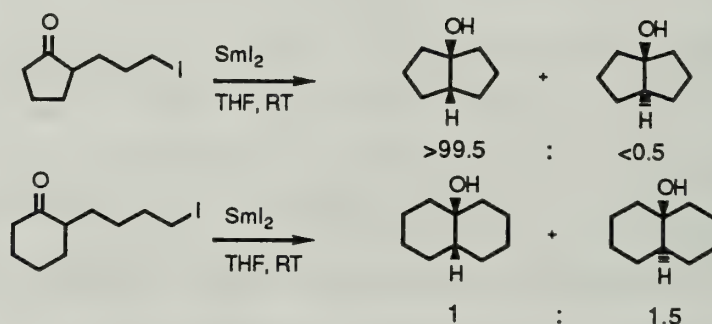


### Intramolecular Reactions

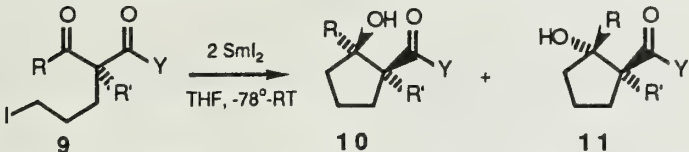
Molander has studied extensively the use of samarium diiodide in intramolecular ketone-halide couplings. He found that bicyclic alcohols could be formed in good yield from the reaction of 2 equivalents of samarium diiodide with iodoalkyl cyclohexanones.<sup>14</sup> Some examples are shown in Scheme IV.

In five-membered ring closures, good stereoselectivity was shown by the predominant formation of the cis ring fused products. Formation of larger rings proceeded in good yields, but the stereoselectivity was greatly diminished. Despite this, these reactions do form six and seven-membered fused rings which are difficult to synthesize using magnesium, alkali metals, or similar reagents.<sup>15</sup>

Scheme IV



Molander has also used samarium diiodide to form functionalized cyclopentanols with high degrees of diastereoselectivity.<sup>16</sup> As shown in Table VI, these reactions provide good yields of five-membered rings with excellent diastereoselectivity. The analogous six-membered rings could not be produced in good yield by this procedure because of hydrogen abstraction by the ketyl radical anion, which has been shown to be a competing process.

Table VI: Diastereoselectivity of  $\text{SmI}_2$  Mediated Ring Closures of 9.


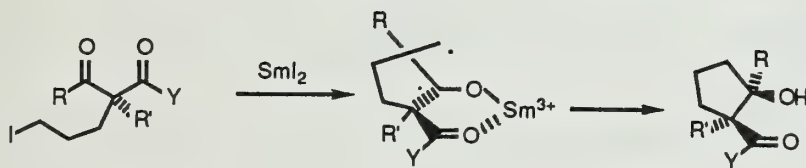
R	R'	Y	% Yield <sup>a</sup>	Ratio (10:11)
Me	H	NEt <sub>2</sub>	80	5.7:1
Me	Me	NEt <sub>2</sub>	91	only 11 detected
Me	Me	OEt	75	36:1
Me	Et	OEt	78	10:1
Et	Me	OEt	81	>200:1

a) Isolated Yields

The amide and ester functionalities are believed to control the stereospecificity of the reaction by chelation, as shown in Scheme V. The molecule is held rigidly and is able to cyclize only to the cis product because of the tight chelation during the kinetically controlled ring closure.

Molander has recently reported the intramolecular reductive coupling of alkenes and ketones using similar methodology,<sup>17</sup> and reductive coupling of ketones with  $\alpha,\beta$ -unsaturated esters<sup>18a,b</sup> and nitriles<sup>18b</sup> has also been reported.

## Scheme V



## Cyclopropanation Reactions

Imamoto found that treatment of  $\alpha$ -haloketones with 3 equivalents of samarium metal and diiodomethane yielded cyclopropanols in good yield (Table VII).<sup>2</sup> The reaction is believed to be occurring through the enolate formed by reduction of the  $\alpha$ -haloketone.

Table VII: Formation of Cyclopropanols from Haloketones.

$  \begin{array}{c}  \text{O} \\  \parallel \\  \text{R}-\text{C}-\text{CH}(\text{R}')-\text{X}  \end{array}  \xrightarrow[3 \text{ CH}_2\text{I}_2]{3 \text{ Sm, THF}}  \begin{array}{c}  \text{R} \quad \text{R}' \\  \diagdown \quad \diagup \\  \text{C} \\  \diagup \quad \diagdown \\  \text{HO}  \end{array}  $			
R	R'	X	% Yield <sup>a</sup>
Ph	H	Br	81
Ph	H	I	88
p-Br-C <sub>6</sub> H <sub>4</sub>	H	Br	67
-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -		Br	81

a) Isolated yields

This is further supported by the fact that treatment of lithium enolates with samarium diiodide and diiodomethane also provides cyclopropanols in moderate yields (Table VIII).<sup>19</sup>

Table VIII: Formation of Cyclopropanols from Lithium Enolates, CH<sub>2</sub>I<sub>2</sub>, and SmI<sub>2</sub>.

Ketone	Product	% Yield <sup>a</sup>
		58
		56
		56
		62

a) Isolated yields

## CONCLUSION

Samarium diiodide has been shown to be a reagent of extreme utility, displaying excellent specificity in many different reactions. It also shows promise as a highly versatile reagent for intramolecular reactions. Samarium diiodide is just beginning to be recognized by organic chemists and thus its full potential has not been realized.



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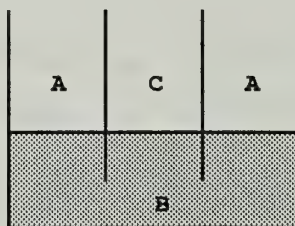
## ENANTIOSELECTIVE TRANSPORT ACROSS LIQUID MEMBRANES

Reported by E. M. Doherty

April 4, 1988

## INTRODUCTION

A liquid membrane is a liquid which acts as a semi-permeable barrier between two phases allowing diffusion of a solute from one phase to the other in a selective fashion. Liquid membranes may be unsupported, as in the case of emulsions and bulk liquid membranes, **Figure 1**, or they may be supported in microporous solids. A high flux can be obtained because the diffusion coefficients of solutes in liquids are typically orders of magnitude greater than in other types of semi-permeable membranes.<sup>1</sup> The addition of a mobile carrier to the liquid, that is, a molecule which facilitates the transport of a solute across the membrane, generally improves both flux and selectivity of the separation.



**Figure 1.** Cross-section of a typical bulk liquid membrane system.

A= receiving solvent, B= liquid membrane, C= solution of racemate.

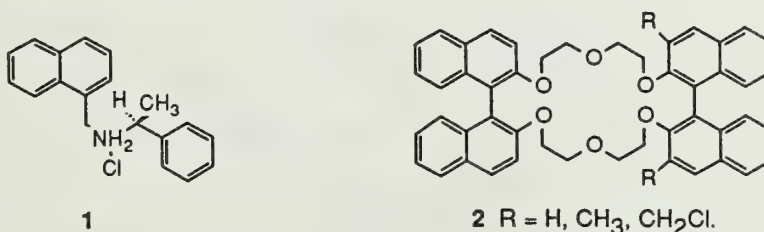
Liquid membranes can be incorporated into continuous separation processes and the cost and energy requirements are often reasonable.<sup>2</sup> For these reasons, liquid membrane resolution of enantiomers is being studied as an alternative to preparative scale chromatography or fractional crystallization of diastereomeric derivatives as a means of obtaining large quantities of optically pure compounds.

This report will address the recent developments in preparative scale resolution of enantiomers by carrier facilitated transport through liquid membranes.

## BACKGROUND

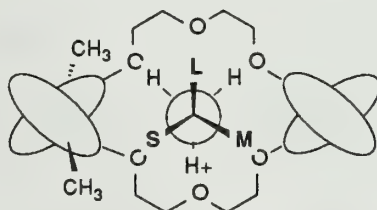
In 1975, Lehn and Behr reported their study of "chiroselective transport" across a liquid membrane.<sup>3</sup> The liquid membrane was chloroform and the carrier molecule was the optically active hydrochloride of (-)-N-(1-naphthylmethyl)- $\alpha$ -phenylethylamine (**1**). The system consisted of the stirred

liquid membrane which separated two water phases, one of which contained racemic sodium mandelate. The best optical resolution obtained was less than 10%, with only 7% of the mandelate transported.



In the meantime, Cram had been investigating some of the applications of crown ethers as complexing agents,<sup>4</sup> following the earlier reports by Pedersen<sup>5</sup> that simple crown compounds had the ability to complex ammonium and alkylammonium salts. Cram designed a chiral crown ether (2) which could distinguish between the enantiomers of the salts of amino acid esters in liquid-liquid chromatography.<sup>6</sup> He then incorporated the same chiral crown ethers into bulk chloroform membranes.<sup>7</sup> Cram referred to the crown ethers as "hosts" and the salts as "guests". Cram, along with Pedersen and Lehn, was awarded the 1987 Nobel Prize for his research on host-guest chemistry.

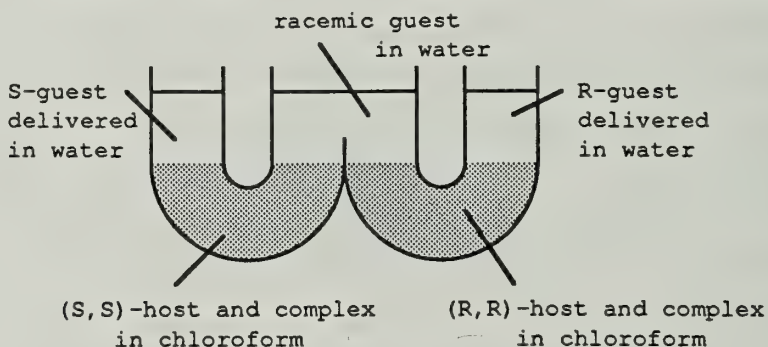
Cram reported a maximum optical resolution of 85% optical purity of the (*R*) enantiomer of *p*-hydroxyphenylglycine methyl ester, with a total transfer of 10% after 182 hours at 24 °C. The results corresponded to the prediction made by examination of the Corey-Pauling-Kolton (CPK) model, **Figure 2**. In it, the amino ester salt is held in the cavity of the host molecule by hydrogen-bonding between the ether oxygens of the host and the amine protons of the guest. The large phenyl group (*L*) extends away from the host, the small hydrogen atom (*S*) is forced toward the methyl-extended naphthalene, and the medium sized group (*M*) is aligned parallel to the face of the naphthalene ring.<sup>8</sup>



**Figure 2.** More stable diastereomer when guest is complexed to methyl-extended chiral crown ether.

Cram and his co-workers then attempted to improve the efficiency of the system by developing a resolving machine.<sup>9</sup> This consisted of a W-shaped tube,

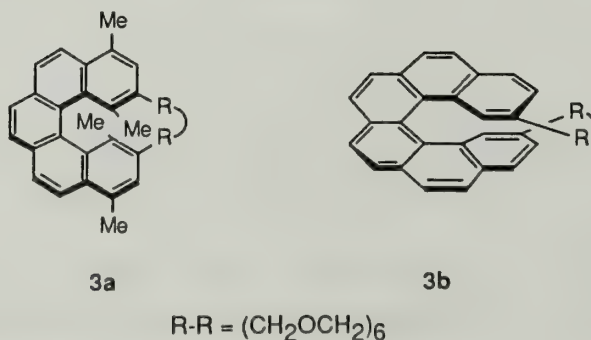
**Figure 3,** containing, in the left arm, the (S,S)- host complex in a chloroform membrane and, in the right arm, the (R,R)- host complex and membrane. The water solution of racemate was central to both membranes and the left arm transported the S-guest while the right arm transported the R-guest. Of 2 runs using phenylglycine methyl ester as guest, between 10 and 20% of either enantiomer had been transported after 25 hours at 23 °C with optical purities in the range of 70-79%.



**Figure 3.** Cram's resolving machine.

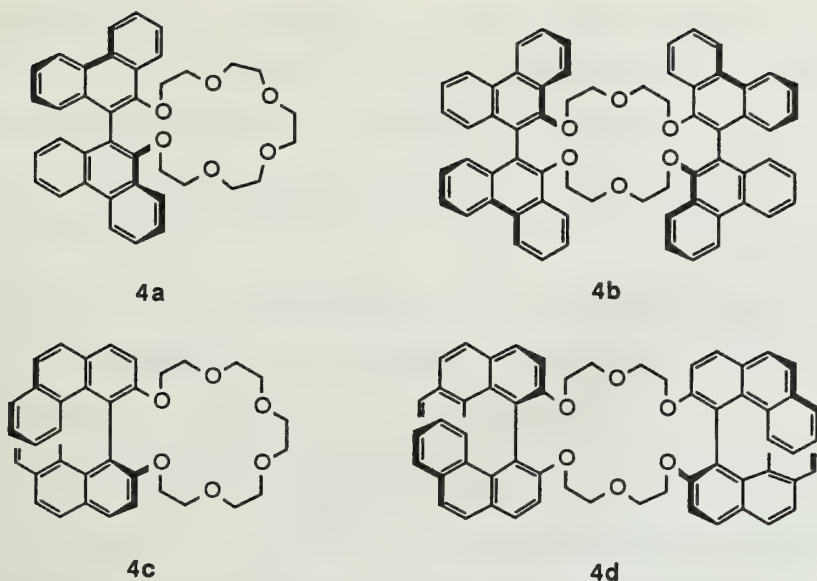
#### RECENT DEVELOPMENTS

From 1983 to 1987 several different types of chiral crown ethers were synthesized by Yamamoto and his co-workers.<sup>10-13</sup> The first of these (3a,b) contained a helicene chiral center.<sup>10</sup> The crown ether was dissolved in a bulk chloroform membrane and the differential transport of the enantiomers of methyl phenylglycinate hydrochloride and  $\alpha$ -phenylethylamine hydrochloride was determined. Optical purities were in the range of 18 to 77% with 2-12% of the guest transported. In the absence of the crown ethers there was no detectable transfer of the guest salts.



The group then synthesized chiral crown ethers (4a-d) which incorporated a biphenanthryl chiral center, employing both the 9,9'- and the 4,4'-biphenanthryl groups.<sup>11,12</sup>





Again, a bulk chloroform membrane was used to determine the differential rate of transport. The enantiomers studied were the hydrochloride salts of methyl phenylglycinate and 1,2-diphenylethylamine. The results of their experiments are listed in Table I.

Table I.

Host	Guest	Time/hr	%Trans <sup>a</sup>	Conf <sup>b</sup>	Purity
(S)-4a	methyl phenyl glycinate	1	2.8	R	24%
(R,R)-4b		24	2.6	S	19%
(S)-4c		0.5	1.4	S	21%
(R,R)-4d		24	2.7	R	25%
(S)-4a	1,2-diphenyl- ethylamine	0.5	2.5	S	32%
(R,R)-4b		12	3.0	R	20%
(S)-4c		0.5	1.6	S	66%
(R,R)-4d		0.5	1.4	R	35%

a. % Trans = % of guest transported through membrane.

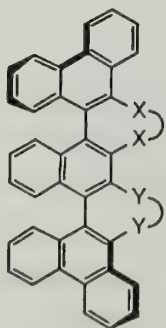
b. Conf = configuration of faster moving enantiomer.

It is interesting to note that the faster moving methyl phenylglycinate enantiomer in the case of hosts 4a and 4b is not that which would be predicted by examination of the CPK model. This problem is not addressed in Yamamoto's report.

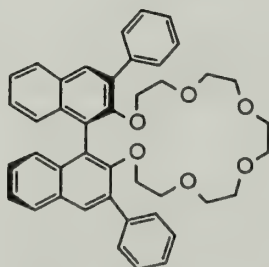
Yamamoto noted also<sup>12</sup> that a decrease in temperature enhanced the enantioselectivity of the separation. He repeated the membrane separation of the enantiomers of 1,2-diphenylethylamine hydrochloride at  $-5^{\circ}\text{C}$  and observed an increase in the optical purity from 32% to 78% when **4a** was the host and from 20% to 23% when the host was **4b**. In both cases the rate of transport increased as well.

Most recently, Yamamoto and his co-workers reported<sup>13</sup> the synthesis of an optically active bis-crown ether (**5**) employing a 1,4-bis-(9-phenanthryl)naphthalene unit as the chiral center. Examination of the CPK model of (*S,S*)-**5** led them to choose potential guest molecules which had two bindable groups, that is, the hydrochloride salts of cystine dimethyl ester and of 1,6-diphenylhexamethylene-1,6-diamine. The behavior of the bis-crown ether toward transport of enantiomers was compared to the behavior of its mono-functional analog. For either guest molecule the rate of transport through a bulk chloroform membrane was enhanced up to 20 times for the bis-ether over the mono-ether. The optical purity of the cystine dimethyl ester was increased from 18% to 66% and that for the diphenylhexamethylenediamine increased from 26% to 82%.

In 1985, Yamaguchi reported the incorporation of a liquid membrane with a chiral crown ether carrier into a microporous polymer film.<sup>14</sup> The crown ether (**6**) was dissolved in 2-nitrophenyl phenyl ether and a polypropylene film was soaked in the solution. The membrane was supported between two aqueous phases and the differential rate of transport of the enantiomers of amino acid perchlorates was studied. The highest enantiomeric excess obtained was 91.6% for the phenylglycine perchlorate. This is the highest enantiomeric excess reported so far for the facilitated enantioselective transport of amino acids across liquid membranes. Yamaguchi was issued a patent for the process in 1986.<sup>15</sup>



**5**  $\text{X-X=Y-Y} = \text{OCH}_2(\text{CH}_2\text{OCH}_2)_4\text{CH}_2\text{O}$

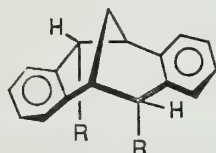
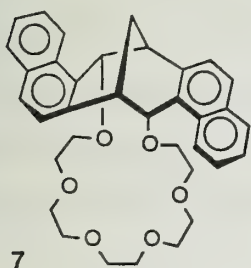


**6**

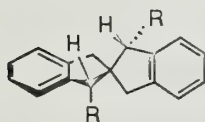
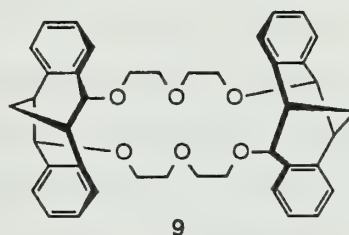
The improvement of Yamaguchi's system over previously reported systems may be accounted for by the fact that his supported liquid membrane had an effective area of interface of  $8 \text{ cm}^2$  while the typical bulk liquid membrane described had an effective area of interface of only  $1.5 \text{ cm}^2$ .<sup>7</sup> It also should be noted that Yamaguchi's experiments involved amino acids while previous groups studied amino esters. The addition of an acidic carboxylic proton may enhance the chiral recognition mechanism. The extended phenyl group on the naphthalene also increases the effect that steric interactions have on chiral recognition.

Yamaguchi also examined the effect that the counter anion had on enantioselectivity. When the counter anion was changed from perchlorate to hexafluorophosphate the rate of transport increased but the enantioselectivity decreased. When the counter anion was nitrate, both rate of transport and selectivity decreased.

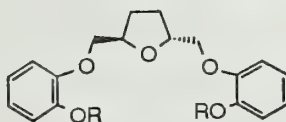
In a series of communications, Naemura reported the synthesis of several novel optically active crown ethers (7-15).<sup>16-20</sup> All of these were examined with respect to their enantioselective transport properties in bulk chloroform membranes. The method was the same as that used by Yamamoto and the enantiomers separated were those of 1,2-diphenylethylamine hydrochloride and methyl phenylglycinate hydrochloride. The best optical purity he reported was 84%<sup>17</sup> using the open-chain polyether (8c).



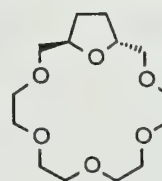
- 8a R-R =  $\text{OCH}_2(\text{CH}_2\text{OCH}_2)_4\text{CH}_2\text{O}$   
 b R-R =  $\text{OCH}_2(\text{CH}_2\text{OCH}_2)_3\text{CH}_2\text{O}$   
 c R =  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$



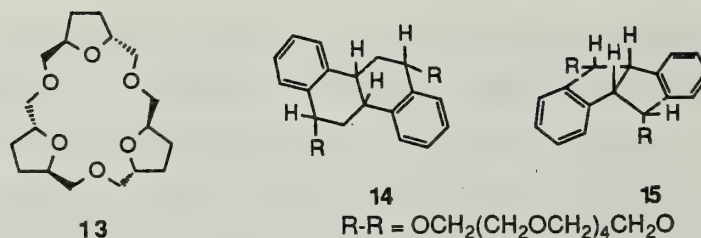
- 10a R-R =  $\text{OCH}_2(\text{CH}_2\text{OCH}_2)_4\text{CH}_2\text{O}$   
 b R-R =  $\text{OCH}_2(\text{CH}_2\text{OCH}_2)_3\text{CH}_2\text{O}$   
 c R =  $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$



- 11a R =  $\text{CH}_3$   
 b R =  $\text{CH}_2\text{CH}_2\text{OCH}_3$   
 c R-R =  $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2$



12



Naemura performed such a large variety of experiments with liquid membranes that it is possible to pick out a few general trends. For instance, the spirobiindandiol-derived chiral crown ethers containing six oxygens (10a) transported the guest salts more rapidly and with higher enantioselectivity than those containing five oxygens (10b).<sup>18</sup> In this case, as well as the case of the crown ethers derived from *trans*-tetrahydrofuran-2,5-diylbismethylene (11-13),<sup>19</sup> the open-chain polyethers performed as well as or better than the cyclic crown ethers.

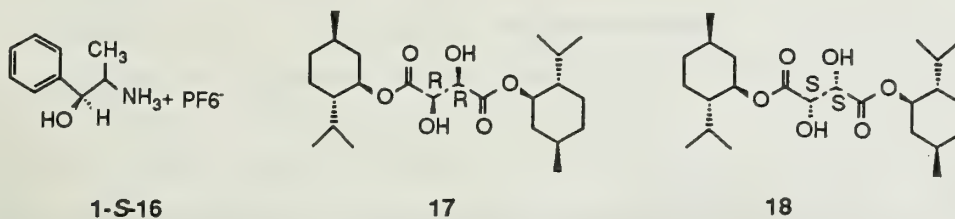
In general, Naemura's experiments indicated that chiral crown ethers incorporating a rigid chiral unit (7-10) showed higher enantioselectivity than the more flexible crown ethers (11-13).<sup>16-19</sup> Further, the enantioselectivity of the crown ether containing a *cis*-tetrahydroindenoindene subunit (15) was enhanced over that of the one containing a *cis*-hexahydrochrysene subunit (14), a slightly less rigid molecule.<sup>20</sup>

Naemura was able, in one case, to improve the optical purity in an experiment by repeating the transport process twice.<sup>19</sup> The aqueous solution containing (*S*)-phenylglycinate of 32% optical purity which was obtained by transport facilitated by crown ether (11b) was re-introduced into the system in place of the racemate. The transport experiment was continued with a fresh aqueous phase replacing the original receiving phase. This procedure was repeated again resulting in a final optical purity of 71%. This process is generally referred to as "staging".<sup>21</sup>

On the other side of the globe, Prelog and his co-workers had been studying the separation of enantiomers by partition between liquid phases in the presence of tartrate esters.<sup>22,23</sup> They then reported the selective transport of norephedrin (16) enantiomers through a bulk dichloromethane membrane in the presence of the lipophilic dimenthyl tartrates 17 and 18.<sup>24</sup> The experiments were run at 0 °C in the apparatus shown in Figure 1 and were stopped after three hours. For tartrate ester 17 a 28% enantiomeric excess of (1-*S*) norephedrin was found in the receiving phase while for tartrate ester 18

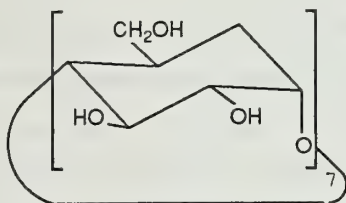


a 14% excess of the (1-R) enantiomer was found. In both cases, approximately 20% of the norephedrin had been transported.



The system that Prelog described has some apparent advantages over those reported by the other researchers. For instance, the tartrate esters were used to resolve a drug which is related to a family of drugs of commercial importance and it is possible that these related drugs may be resolved in the same way. Also, if a staging process were applied to this system, such as that used by Naemura,<sup>19</sup> even greater e.e.'s may have been obtained. Above all, the carrier molecule employed in this process was easily synthesized from commercially available and relatively inexpensive precursors.

Armstrong has recently reported<sup>25</sup> the use of  $\beta$ -cyclodextrin carriers (19) in the enantioselective transport of hydrophobic compounds across aqueous membranes.



The systems were contained in capillary tubes which were sealed at one end while the enantiomer ether solution, liquid membrane and carrier, and neat ether were layered in via syringe. A variety of enantiomers was studied, a representative sampling of which is listed in Table II, and the enantiomeric

Racemate	Enantiomer in Excess	e.e.
phenyl (1-ferrocenyl-ethyl) sulfide	+	75%
(R,S)-1'-benzyl-nornicotine	S	50%
mephénytoin	unknown	20%

excesses were in the range of 16-75%. Though Armstrong was forced to do very small scale separations due to the limited supply of racemate, his results indicate that liquid membrane-type resolutions can be expanded to include lipophilic substrates along with the hydrophilic substrates previously studied.

## CONCLUSION

Since the ground-breaking work done in this area by the Lehn and Cram groups, many others have contributed to the technology of liquid membrane-based resolution of enantiomers. Some general conclusions can be made. First, the mobile carrier-substrate interactions can be tailored to enhance specific separations. Second, the incorporation of liquid membranes into thin microporous supports as well as the application of staging to the process can result in separations of very high enantiomeric excess. Finally, liquid membrane-based resolutions are not limited to those involving diastereomeric salt formation but can include also the transport of uncharged, lipophilic species. It has yet to be determined whether these procedures can be done on a preparative scale.

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# REGIOCHEMISTRY OF THE REACTIONS OF HETEROSUBSTITUTED ALLYL ANIONS WITH ELECTROPHILES

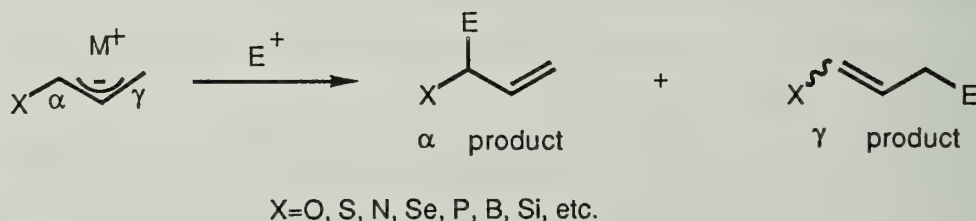
Reported by Won Koo Lee

April 7, 1988

## INTRODUCTION

There has been considerable interest in allyl anion chemistry. These formal anions play an important role in many organic reactions. However, the problem in applying this chemistry to organic synthesis is controlling the site of the reaction of unsymmetrically substituted allyl anion with electrophiles. This regioselectivity problem is illustrated with a 1-substituted allyl carbanion for reactions with various electrophiles in Scheme I. The question of the ratio of  $\alpha$  and  $\gamma$  products has drawn theoretical and synthetic interest.<sup>1</sup>

### Scheme I



The regiochemistry of the reactions of 1-hetero-substituted anions depends on many factors including the electrophile,<sup>2</sup> substituent,<sup>3</sup> counterion,<sup>4</sup> and solvent system.<sup>5</sup> There seems to be no consistent pattern to the observed regiochemistry. It does seem that carbonyl compounds and alkyl halides often react at different sites of hetero-substituted allyl anions. Control of the regiochemistry of the reaction site has great importance for the synthetic use of these reactions.

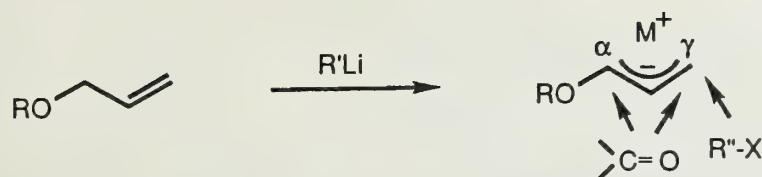
In this abstract the regiochemistry of 1-heteroatom(X=O, S, N)-substituted allyl anions will be discussed.

### 1-OXYGEN-SUBSTITUTED ALLYL ANIONS (X=O)

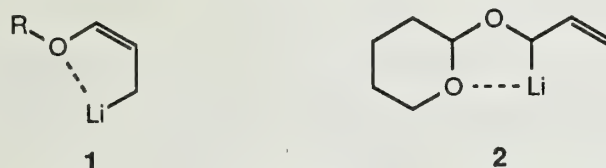
Simple allylic ethers can be metalated at low temperatures. In general, carbanions from allylic ethers show different regioselectivity in reaction with alkyl halides, which favor the  $\gamma$  products, and carbonyl compounds, which favor both the  $\alpha$  and  $\gamma$  products. This is shown in Scheme II.<sup>6</sup>



## Scheme II

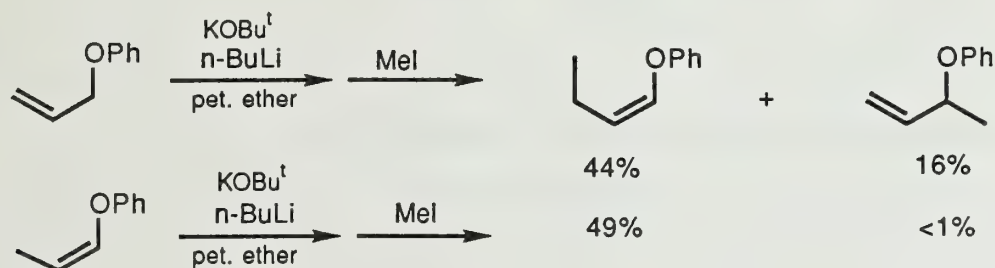


Evans studied steric effects of oxygen substituents in the alkylation reaction of allyl alkyl ethers and found that bulkier alkyl groups gave more  $\gamma$ -substitution product.<sup>7</sup> Similar regioselectivity was obtained with allyl triethylsilyl ethers.<sup>8</sup> Analysis of the  $\gamma$ -alkylation product showed that there was no *trans* enol ether. The double bond stereoselectivity may be explained by the formation of a five-membered chelate ring of the allyl anion(1).<sup>9</sup> The chelation effect was also apparent for tetrahydropyranyl allyl ether where the lithium was presumed to be chelated at the  $\alpha$ -position



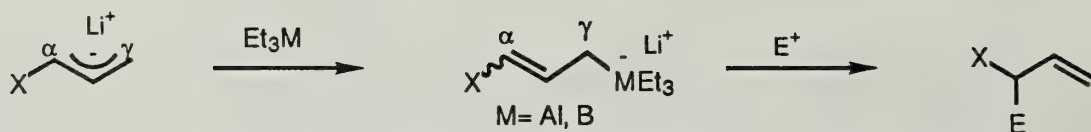
(2); this gave nearly entirely  $\alpha$ -alkylation product.<sup>10</sup> The importance of chelation can be seen in the alkylation of phenyl allyl ether and of phenyl (*Z*)-1-propenyl ether, which gave different product ratios (Scheme III).<sup>11</sup>

## Scheme III



In 1984, Yamamoto and coworkers prepared allylic aluminum and boron "ate" complexes by adding, before treatment with an electrophile, triethylaluminum or triethylboron to allylic anion solutions in which the X substituent was an isopropoxy or methoxymethoxy group. They showed that they could direct both carbonyl compounds and reactive alkyl halides to the  $\alpha$ -position with very high regioselectivity (Scheme IV).<sup>6d</sup> Both the aluminum

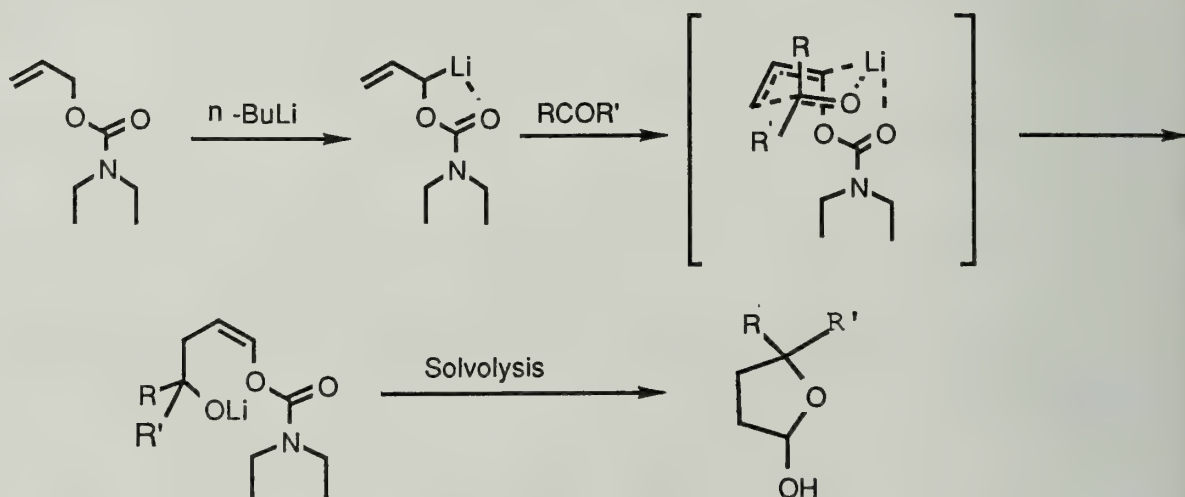
## Scheme IV



and the boron "ate" complexes usually give very high regioselectivity, they do not react with simple alkyl halide such as methyl iodide and *n*-butyl iodide.

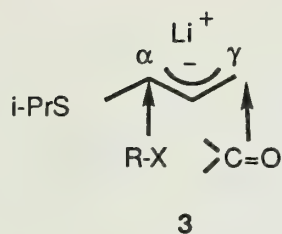
The opposite regioselectivity was shown in 1983 by Hoppe and coworkers for the case in which X is the *N,N*-diethylcarbamate group. In most reactions, the anion from allyl *N,N*-diethylcarbamate showed better than 95% γ-selectivity with carbonyl compounds to give enol carbamates which could be hydrolyzed to lactols as shown in Scheme V.<sup>12</sup>

## Scheme V



## 1-SULFUR-SUBSTITUTED ALLYL ANIONS (X=S)

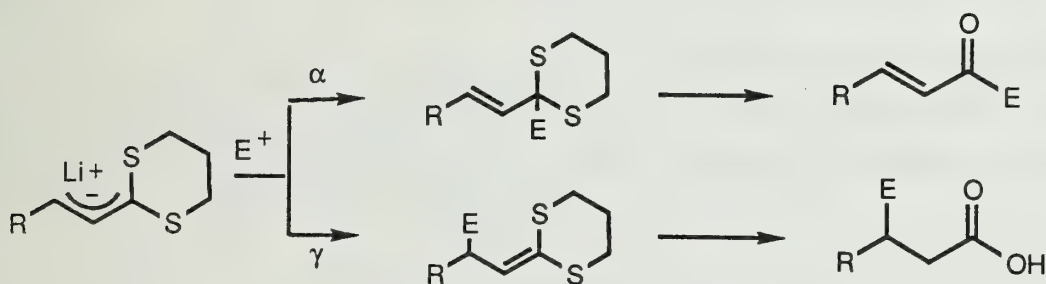
The (alkylthio)allyl carbanions show different regioselectivity from that of (alkyloxy)allyl carbanions. When they react with alkyl halides, α-products are formed selectively, whereas with carbonyl compounds γ-products are formed selectively (3).<sup>13</sup> Here again, one gets high regioselectivity at the α-position with both carbonyl compounds and allylic halides if one prepares triethylaluminum or triethylboron "ate" complexes of the anions before treatment with electrophiles.<sup>6d</sup> The aluminum "ate" complexes usually give higher regioselectivity with ketones than boron "ate" complexes. Steric



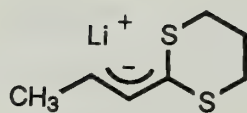
hindrance may explain this phenomenon. The C-Al bond length is longer than the C-B bond, which gives less steric hindrance at the  $\alpha$ -carbon. Another explanation is the difference in bond character of C-Al and C-B bonds; the C-Al bond has more ionic character, which may facilitate the reaction with carbonyl compounds.<sup>14</sup> The amount of the triethylaluminum complexing agent also plays an important role in determining regioselectivity. When the reagent used was less than one equivalent of the anion, there was a marked decrease in the regioselectivity, whereas an excess of the additive did not influence the selectivity.<sup>6d</sup>

A 1,1-dithio-substituted allylic anion is synthetically equivalent to an  $\alpha,\beta$ -unsaturated acyl anion if the anion has  $\alpha$ -selectivity with electrophiles, whereas the anion can function as an equivalent of the  $\beta$ -anion of a carboxylic acid if the anion has  $\gamma$ -selectivity with electrophiles (Scheme VI).

#### Scheme VI



Recently, very high regioselectivity in the reaction between dithio-substituted crotyllithium (**4**) and carbonyl compounds was reported.<sup>15</sup> This anion gives the  $\alpha$ -product exclusively with deuterium oxide, iodomethane, and chlorotrimethylsilane, but aldehydes react dominantly at the  $\gamma$ -position (Table I). This high regioselectivity with aldehydes can be explained by a

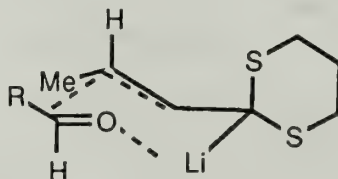


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Table I. Reaction of Crotyllithium, 4, with Aldehydes and Simple Ketones

Electrophile	Products Ratio ( $\alpha:\gamma$ )	Yield (%)
Acetaldehyde	<5:95	86
Propionaldehyde	<5:95	91
Isobutyraldehyde	<5:95	93
Acrolein	<1:100	87
Benzaldehyde	<1:100	92
Cyclopentanone	100:<1	85
Cyclohexanone	82:18	92
4- <del>t</del> -Butylcyclohexanone	80:20	90
Cycloheptanone	100:<1	86
2-Butanone	84:16	93
3-Pentanone	85:15	91
2-Heptanone	92: 8	92

chair-like transition state (5) with chelation. However, when the anions react with modest-sized ketones, the major reaction takes place at the  $\alpha$ -position (Table I), but with bulky ketones the reaction takes place at the



5

$\gamma$ -position exclusively (Table II). It is not easy to explain these experimental results by steric effects alone. Another explanation is based on the principle of hard and soft acids and bases (HSAB).<sup>16</sup> However, this HSAB theory does not always explain the regioselectivity when steric factors are involved in the reaction.



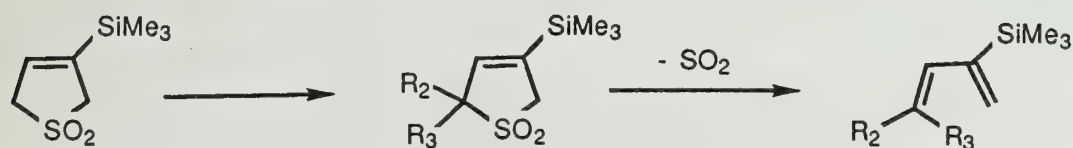
Table II. Reaction of Crotyllithium with Bulky and Unsaturated Ketones

Electrophile	Ratio ( $\alpha$ : $\gamma$ )	Yield(%)
Diisopropyl ketone	<1:100	32
Ethyl pyruvate	<1:100	86
Acetophenone	<1:100	91
Benzophenone	<1:100	93
2-Cyclopentenone	100:<1	89
2-Cyclohexenone	44:56	86
Methyl vinyl ketone	<1:100	87
Mesityl oxide	<1:100	90

Anions can be generated from allylic sulfoxides. It was shown recently that lithiated allylic sulfoxides gave exclusively the 1,4-addition product with cyclopentenone and related substrates at the  $\gamma$ -position,<sup>17,18</sup> but reaction with aldehydes did not give regioselectivity in the absence of a complexing agent. In these reactions, substantial amounts of complexing agent are required to get good  $\alpha$  selectivity and, among those complexing agents, hexamethylphosphoramide gave the best  $\alpha$  regioselectivity. Using metals softer than lithium (e.g., magnesium, zinc, or cadmium) increased the  $\gamma$  adduct.

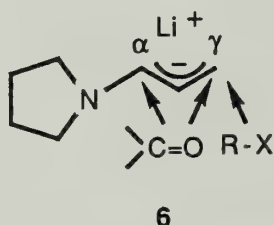
Sulfones can also stabilize an anion<sup>19,20</sup> and can be removed easily after the reaction. Therefore, the use of sulfones in natural products chemistry has increased considerably in recent years.<sup>21,22</sup> Sulfone-substituted lithiated allyl anions give  $\alpha$ -alkylated products with alkyl halides.<sup>1c</sup> Recent studies show that substituted allylic sulfones can undergo 1,3-rearrangement,<sup>23-26</sup> and a cyclic sulfone, 3-(trimethylsilyl)-3-sulfolene, can be used as a precursor of 2-silyl-1,3-butadiene derivatives, which are useful in the Diels-Alder reaction (Scheme VII).<sup>27</sup>

#### Scheme VII



# 1-NITROGEN-SUBSTITUTED ALLYL ANIONS (X=N)

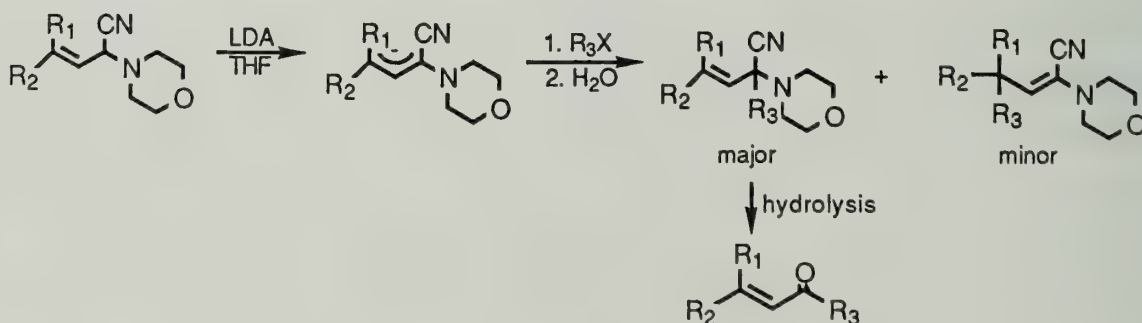
Allyl anions with  $\alpha$ -nitrogen substituents can also be used as homoenolate equivalents if the anions react with electrophiles at the  $\gamma$  position.<sup>28</sup> Unlike the oxygen- and sulfur-substituted allyl anions, nitrogen-substituted anions show quite low regioselectivity with carbonyl compounds, but the pyrrolidine-substituted allyl anion reacts with alkyl halides and chlorotrimethylsilane at the  $\gamma$  position(6).<sup>29</sup> This regioselectivity can also be improved by treating the anion with triethylaluminum or triethylboron before adding the electrophile. When



chlorotrimethylsilane was used as an electrophile, the anion gave the  $\alpha$  adduct as the major product, but reaction with carbonyl compounds resulted in a mixture of products.

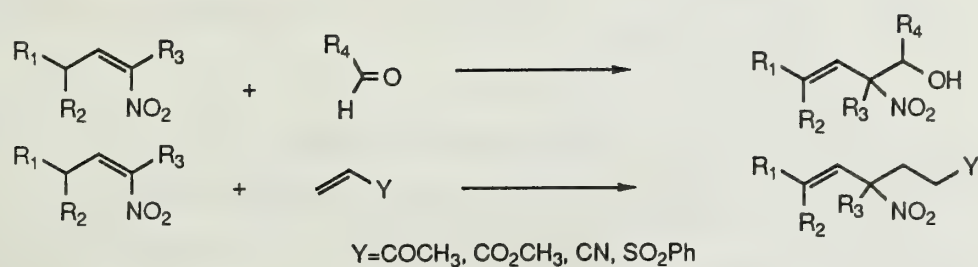
Takahashi and coworkers showed that the anion from 2-morpholino-3-butenenitrile can be an  $\alpha,\beta$ -unsaturated acyl anion equivalent (Scheme VIII).<sup>30</sup>

## Scheme VIII



Anions from  $\alpha,\beta$ -unsaturated nitro compounds also gave good  $\alpha$  regioselectivity with aldehydes or electron-deficient olefins (Scheme IX)<sup>31</sup>, although the selection of base was important. Various aldehydes reacted with the anion to give the  $\alpha$ -product when  $R_3=H$  but when  $R_3$  was not hydrogen only formaldehyde reacted and it gave the  $\alpha$  product.

## Scheme IX



Another nitrogen-substituted allylic system investigated consists of allyl amides. Some tertiary and secondary amides mainly gave the  $\gamma$ -substituted product from metalation followed by electrophilic substitution.<sup>32</sup>

**CONCLUSION** Although allyl anion chemistry has been studied for a long time, adequate information is lacking regard the transition state structure of the anions. The most successful way to control the regioselectivity of 1-hetero-substituted allyl anions has been to change the counter ion. By employing an appropriate substituent in the allylic system and by modifying the reaction conditions, the regiochemistry of allylic anions can be controlled, but with some limitation.

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# SYNTHESIS AND ACTIVITY OF PEPTIDE-BOND ISOSTERES

Reported by James DiZio

April 11, 1988

## INTRODUCTION

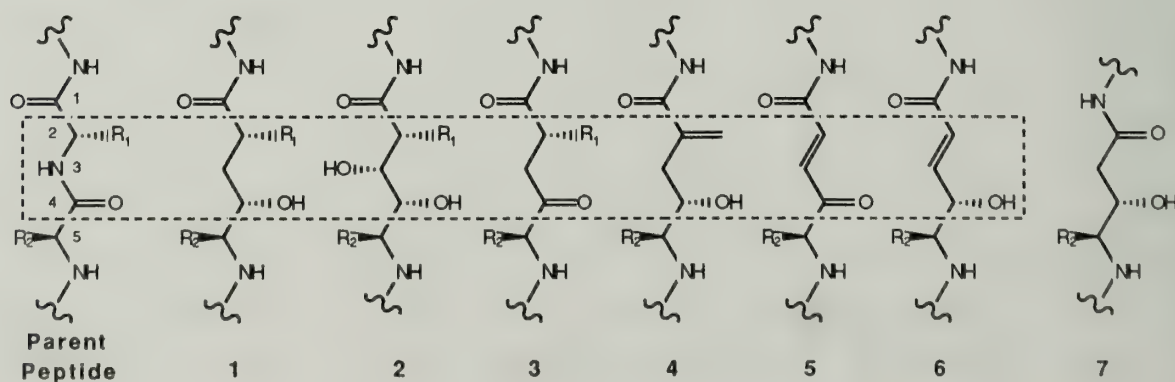
A peptide-bond isostere is, in the most general sense, any unit that serves to substitute for the amide bond. A review of the literature concerning peptide backbone modifications was published in 1983 by Spatola.<sup>1</sup> Covered in the present report is the formidable array of peptide isostere units currently under investigation.

The main reason to replace the amide bond is to protect the peptide against enzymatic hydrolysis. Peptide bond isosteres may also serve to change the local or total polarity, increase the selectivity and change agonistic vs. antagonistic activities of the parent peptide.<sup>2a</sup> Overcoming therapeutic limitations of peptides such as poor oral absorptivity and marginal ability to cross biomembranes are ultimate goals for the use of peptide isosteres.<sup>3a</sup> Improved syntheses of many isosteric units have appeared within the last few years which have aided in the development of enzyme inhibitors and in the elucidation of the role of individual peptide bonds in biologically active peptides.

## DESCRIPTION AND SYNTHESIS

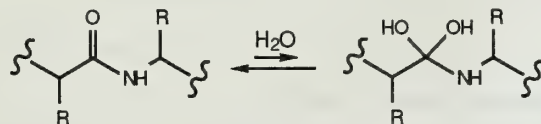
### Hydroxyethylene and Hydroxyethylene analogs

Included in this category are the hydroxyethylene (1), dihydroxyethylene (2), ketomethylene (3), dehydrohydroxyethylene (4), ketovinyl (5), and hydroxyethylidene (6) peptide isosteres.



The current focus of interest on pseudopeptide units **1** to **6** is in part due to their similarity (at C-3 and C-4) to the unusual amino acid statine **7**, which is found in the naturally occurring pentapeptide inhibitor pepstatin.<sup>4</sup> The statine residue has been proposed to be an analog for the tetrahedral intermediate formed during the enzymatic hydrolysis of a peptide bond (Scheme I).<sup>5</sup> The possibility that these types of isosteres serve as transition state analogs of their parent peptides has been discussed fully by Rich.<sup>6</sup>

Scheme I



The dihydroxyethylene pseudopeptide unit **2** was developed in an attempt to create a transition state analog that was tighter binding than the hydroxyethylene unit.<sup>7</sup> It was felt that these compounds could better mimic the tetrahedral intermediate shown in Scheme I. The ketomethylene pseudopeptide unit **3**, which can be obtained by way of the hydroxyethylene unit and is usually compared with the hydroxyethylene isosteric unit, retains most of the hydrogen bonding and complexing<sup>8a</sup> abilities of the parent peptide, although planarity is lost.<sup>1</sup>

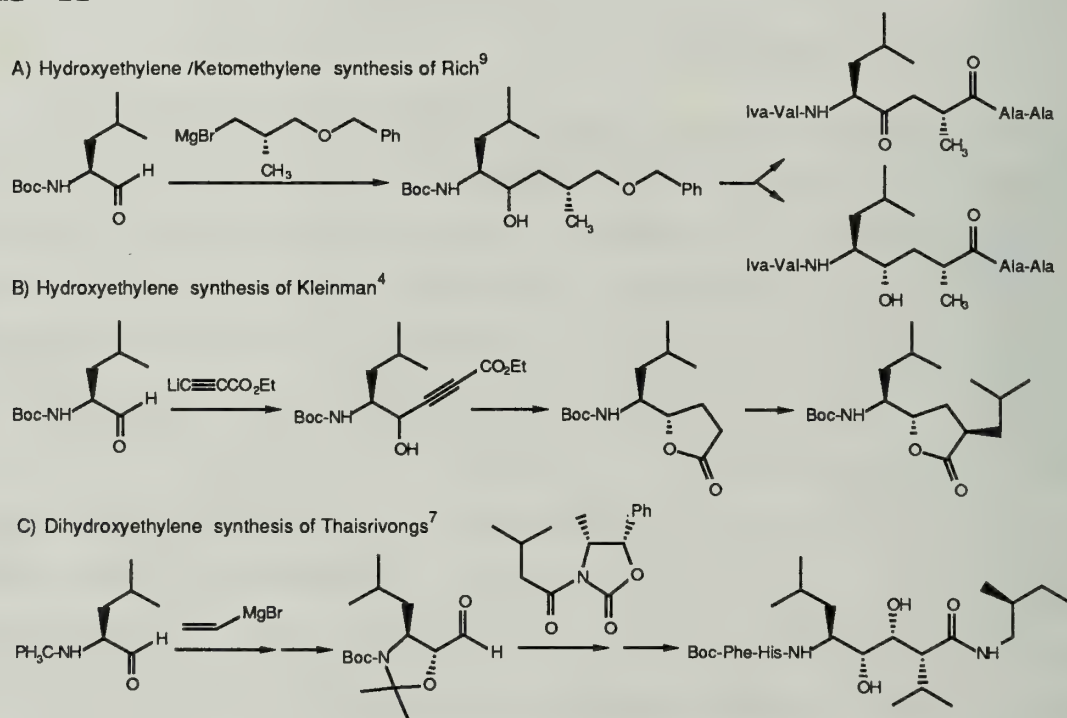
Syntheses of hydroxyethylene (**1**), ketomethylene (**3**), and dihydroxyethylene (**2**) isosteres are shown in Scheme II. The only current syntheses for the ketomethylene peptide isosteric unit are those developed by Ewenson et al.<sup>8a</sup> and by Rich et al.<sup>9</sup> The better procedure<sup>9</sup> will be covered as a part of the overlapping hydroxyethylene synthesis.

Although notable syntheses of hydroxyethylene dipeptide units have been published,<sup>10,11</sup> the syntheses that imparted reasonable stereochemical control at C-2, C-4, and C-5 were those of Rich et al.<sup>9</sup> and Kleinman et al.<sup>4</sup> Both methods (summarized in Scheme II) use readily available amino acids, which are then converted to the protected amino aldehydes, as the source of R<sub>2</sub>, C-4, and C-5. Rich and coworkers<sup>9</sup> introduced an optically active C-1 to C-3 fragment as a Grignard reagent adding to N-Boc-L-leucinal, yielding a 4:1 ratio of the desired *S* to the undesired *R* epimer. Further elaboration of the peptide yielded the hydroxyethylene or the ketomethylene pseudopeptide. Kleinman and coworkers<sup>4</sup> introduced the anion of ethyl propiolate as a homoenolate equivalent adding to N-Boc-L-leucinal. Subsequent hydrogenation and ring closure afforded a lactone in a 1:4 (*R*, undesired:*S*, desired) ratio. R<sub>2</sub> was introduced by stereoselective alkylation of the lactone followed by

hydrogenation to afford the precursor to the 2*R*,4*S*,5*S* hydroxyethylene dipeptide isostere of Leu-Leu. The precursor can be elaborated through the method of Evans et al.<sup>10</sup>

Preparation of the dihydroxyethylene isostere began by the addition of a vinyl Grignard reagent to a protected L-leucinal.<sup>7</sup> Ozonolysis afforded C-3 as an aldehyde that was subsequently subjected to stereocontrolled aldol addition to an acyloxazolidinone. Further elaboration afforded the renin inhibiting dihydroxyethylene peptide isosteres.

## Scheme II



Dehydrohydroxyethylene (4), ketovinyl (5), and hydroxyethylidene (6) isosteres (seen in Scheme III) serve as analogs that can act as possible site directed alkylating agents. Dehydrohydroxyethylene isosteres were formed via a metalation strategy linking a  $\beta'$ -lithiated<sup>12b</sup> N-isobutylmethacrylamide to a protected amino aldehyde.<sup>12a</sup> Manipulation of the  $\alpha,\beta$ -unsaturated amide (for example, by epoxidation) also afforded derivatives useful for study. Ketovinyl, and hydroxyethylidene isosteres were prepared by treatment of a protected L-phenylalaninal with vinylmagnesium bromide followed by ozonolysis and then treatment with (carbethoxymethylene)triphenylphosphine.<sup>13</sup>

## Iminomethylene

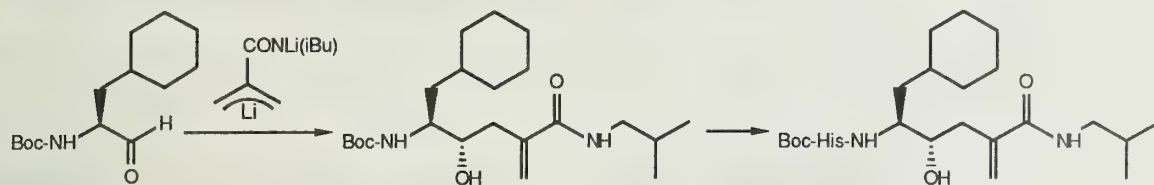
The iminomethylene "reduced peptide bond" (8)<sup>14</sup> offers some possible advantages over the parent peptide bond. The secondary amine function adds a



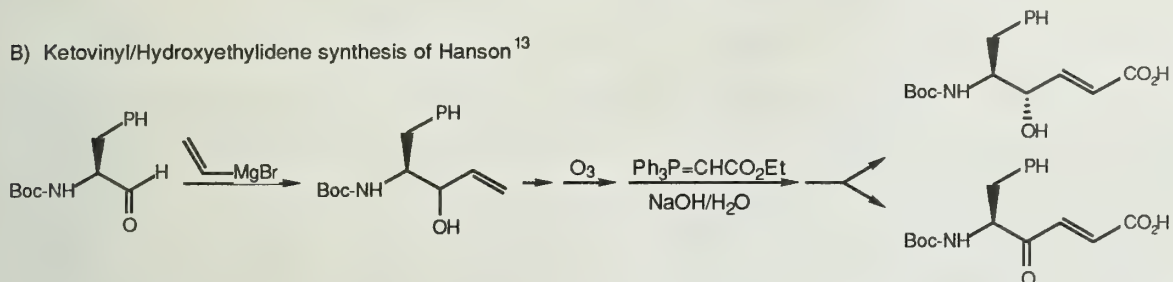
new base and ionizable site to the peptide which could interact with the receptor and also aid in the solubility of lipophilic peptides.<sup>1</sup> The

### Scheme III

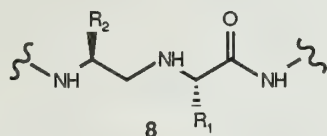
#### A) Dehydrohydroxyethylene synthesis of Kempf<sup>12a</sup>



#### B) Ketovinyl/Hydroxyethylidene synthesis of Hanson<sup>13</sup>



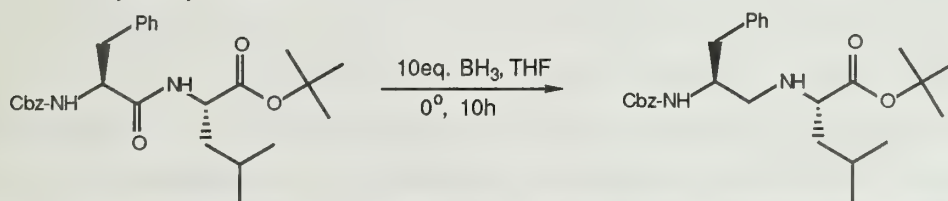
$sp^3$  centers of this pseudopeptide unit help to mimic the tetrahedral intermediate of the hydrolyzing parent peptide (Scheme I).



Three different approaches have been used to synthesize iminomethylene pseudopeptides.<sup>15,16,14,17a</sup> The most general of these methods is outlined in Scheme IV. Ueki and coworkers reinvestigated a direct reduction approach<sup>17b</sup> and developed a general method for the transformation of a peptide bond into an iminomethylene bond.<sup>17a</sup> The method involves the selective reduction of N-protected dipeptides esters by diborane. A leu-enkephalin was synthesized in

#### Scheme IV

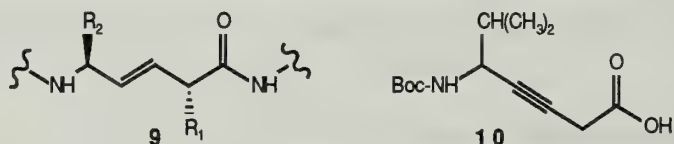
##### Iminomethylene synthesis of Ueki<sup>17a</sup>



good yield from the iminomethylene dipeptide unprotected at the secondary amine. Other strategies involved aziridine ring opening with aminoesters,<sup>15a</sup> or allowing an N-protected amino aldehyde to react with the amine of a protected peptide in the presence of sodium cyanoborohydride.<sup>14,16</sup>

### **Trans-Alkene and Acetylene**

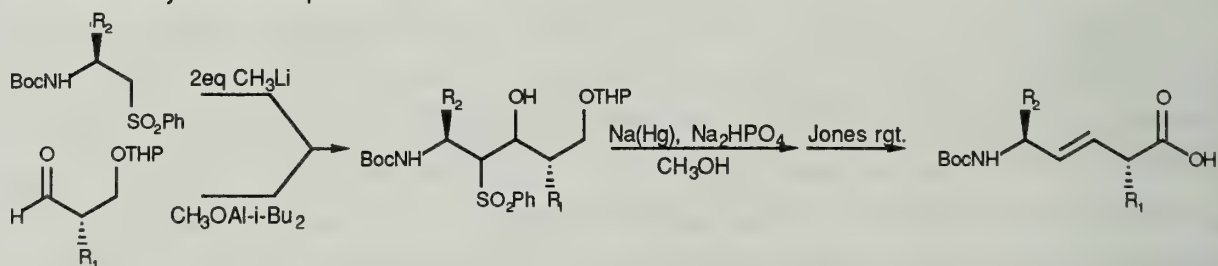
The *trans* carbon-carbon double bond closely mimics the three-dimensional shape of the amide bond and, therefore, the *trans*-alkene isostere **9** represents an excellent analog to the peptide bond.<sup>18a</sup> An acetylene peptide bond isostere **10** has also been prepared, although no studies on pseudopeptides incorporating this isostere have yet been performed.<sup>19</sup>



There are three currently employed methods for the synthesis of the *trans*-alkene isostere,<sup>20,3a,21</sup> but only the procedure of Hopkins and coworkers<sup>21</sup> provides a fully stereocontrolled route (Scheme V). The strategy employs the coupling of N-protected  $\beta$ -amino sulfones to protected  $\beta$ -hydroxy aldehydes. Appreciable racemization did not occur in the synthesis, nor was the *cis* double-bond isomer detected. A negative charge on the  $\gamma$ -nitrogen of the sulfone starting material is necessary to avoid  $\beta$ -elimination forming the vinyl sulfone. Because of this limitation, the proline analog of the starting material cannot be accommodated in this procedure.

#### **Scheme V**

*Trans* - Alkene synthesis of Hopkins<sup>21</sup>

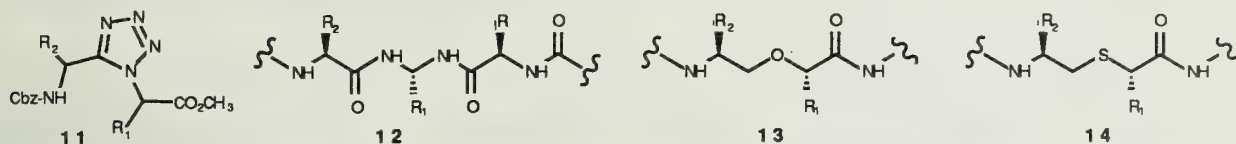


#### **General**

Literature can also be found on other notable peptide bond isosteres such as the tetrazole (**11**),<sup>22</sup> retro-inverso (**12**),<sup>23,24</sup> methyleneoxy (**13**),<sup>15,25,2a</sup> and methylenethio (**14**)<sup>1,15</sup> replacements.

The tetrazole replacement is meant to mimic the *cis* amide bond. The retro-inverso replacement involves the reversal in sequence of the peptide bond along with an inversion at chiral centers. The methylenethio isosteric unit has been proposed to display reasonable isosterism, and facile syntheses have been known for some time.<sup>1</sup> Geometrical analysis of the methyleneoxy/thio isosteric units in the extended conformation showed that

the methyleneoxy isostere better represented the parent peptide geometry than did the methylenethio isostere.<sup>2a</sup>



## ACTIVITY

A peptide-bond isosteric unit can serve either as a probe to deduce the relative importance of a specific peptide bond, or as a hydrolytically resistant bond placed strategically at the scissile site of a peptide sequence. Inhibition of enzymatic processes can occur due to the resistance at a scissile site of the pseudopeptide. Currently, the most widely employed peptide-bond isosteric units are the *trans*-alkene, iminomethylene, analogs of hydroxyethylene, and hydroxyethylene pseudopeptides.

### Hydroxyethylene and Hydroxyethylene Analogs

Thaisrivongs et al.<sup>26</sup> developed a hydroxyethylene isostere as a potent human renin inhibitor ( $IC_{50}$   $0.26 \times 10^{-9}M$ ) that showed metabolic stability, high specificity for renin as compared to other aspartyl proteases, and the ability to lower the blood pressure of sodium-depleted cynomolgus monkeys for an extended period. Rich and coworkers<sup>9</sup> studied the effects of pepstatin analogs containing hydroxyethylene or ketomethylene isosteric units vs pepstatin on the inhibition of porcine pepsin. The residue  $leu\psi[CHOHCH_2]ala$  (where the symbol  $\psi[CHOHCH_2]$  represents that the hydroxyethylene unit,  $-CHOHCH_2-$ , has been substituted for the normal peptide unit,  $-CONH-$ ) was found to be a statine analog. Potent inhibitors, incorporating the ketomethylene unit, of substance P degrading peptidases<sup>8a,b</sup> and angiotensin converting enzyme (ACE)<sup>27a,b</sup> have also been created. The ACE inhibitors showed no effect on the blood pressure or heart rate of renal hypertensive rats. This was presumably due to rapid excretion into the bile. The dihydroxyethylene peptide isosteres were potent inhibitors of human renin, although they afforded no measurable enhancement over analogous hydroxyethylene isosteres. This illustrated the importance of the hydroxyl group at C-4 and the relative inertness of the hydroxyl at C-3. The dehydrohydroxyethylene modified peptides were also found to be potent renin inhibitors ( $IC_{50}$   $0.8-2.0 \times 10^{-9}M$ ),<sup>12a</sup> although studies showed that irreversible binding did not occur with these peptide isosteres.



### **Iminomethylene**

Martinez and coworkers performed studies on analogs of the C-terminal tetrapeptide of gastrin<sup>28</sup> and C-terminal heptapeptide of cholecystokinin<sup>14</sup> (CCK). Replacing individual peptide bonds with an iminomethylene bond in the gastrin analogs afforded pseudopeptides with high affinity for the gastrin receptor. Agonistic or antagonistic behavior toward acid secretion was noticed, depending on the particular peptide bond affected. On the other hand, replacing individual peptide bonds with an iminomethylene bond in CCK analogs led to a conclusion that the peptide bonds are not critical to the affinity towards its respective pancreatic or brain CCK receptors. Neither did the CCK peptide bonds appear critical towards activity (amylase release). Coy et al.<sup>16</sup> found minimal success at attaining iminomethylene analogs of a potent somatostatin octapeptide with greater or equal growth hormone release inhibitory characteristics. Szelke and coworkers produced many iminomethylene pseudopeptides in an effort to obtain human renin inhibitors. One such pseudopeptide, H-142, was found to have potent renin inhibitory properties ( $IC_{50}$   $10.0 \times 10^{-9}M$ ).<sup>29</sup>

### **Trans-alkene**

This type of isostere is mainly used as a probe to distinguish a critical from a non-critical peptide bond. *Trans*-alkene analogs of renin inhibitors,<sup>3b</sup> enkephalins,<sup>18a,b</sup> and substance P<sup>18b</sup> have been synthesized for structure activity relationships. In cases where biological activity remained relatively equivalent to the parent peptide, a conclusion was drawn that the affected amide bond acts only as a spacer. In cases where biological activity dropped noticeably, the conclusion was that the amide bond is most likely essential to biological activity, in terms of hydrogen bonding to itself or to the enzyme. No cases of greatly increased activity were found.

### **General**

Methyleneoxy and methylenethio isosteres of vasopressin displayed the ability to reverse electroconvulsive shock induced amnesia in rodents.<sup>15</sup> In this study the isosteres were generally less active than the parent peptides. Methyleneoxy analogs of substance P and enkephalin have also been studied.<sup>2b,c</sup> Retro-inverso analogs of gastrin<sup>23</sup> and enkephalin<sup>24</sup> have recently been prepared. The gastrin analogs were very potent in inhibiting gastrin-promoted acid secretion.



## CONCLUSION

The field of peptide replacements is a growing one, with new synthetic methods paving the way. As more data are acquired, it will become more evident as to which isostere unit would best fit a particular need. At this time, researchers have shown the usefulness of peptide bond isosteres as probes and enzyme inhibitory agents.

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## POLYMER SUPPORTED REAGENTS

Reported by C. B. W. Senanayake

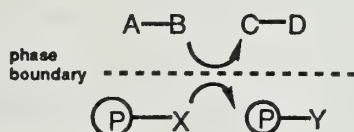
April 14, 1988

## INTRODUCTION

The invention of solid phase polypeptide synthesis by Merrifield<sup>1</sup> has stimulated a number of chemists to use polymer supports for various synthetic transformations. The advantage of solid phase peptide syntheses is that a polypeptide is synthesized in a repetitive sequential manner on the solid phase and the final products are liberated from the polymer in a final cleavage reaction.

The advantage of a polymer assisted reaction is that the polymer supported reagent is usually insoluble or easily (Scheme I) precipitated, which facilitates easy work-up as well as recycling of the polymer supported reagent. In favorable cases the reaction work-up just involves filtration of the polymer from the liquid phase. Another advantage accrues from the insolubility and involatility of the polymer, in that polymer supported reagents will be non-toxic and odorless.

Scheme I



A functionalized polymer is a synthetic macromolecule to which are chemically bound functional groups which can be utilized as reagents, catalysts, protecting groups, chiral auxiliaries etc. The macromolecule can be a linear species capable of forming a molecular solution in a suitable solvent or a cross-linked species, which can be solvated by a suitable solvent. Two main routes are available for the preparation of functionalized polymers - copolymerization of reactive polymers and chemical modification of preformed polymers or copolymers. A difficulty associated with copolymerization is that a good copolymerization procedure may be necessary to ensure a good yield of desired polymer. In the chemical modification procedure commercially available resins of high quality are normally used and the desired functional group is introduced by using standard organic synthetic transformations. Even though this procedure ensures a product with a good



physical form, rarely does it allow for every repeating unit to be functionalized.

Functionalized polymer support must possess a structure which permits adequate diffusion of substrates into the reactive sites. This depends on the extent of swelling or solvation, the effective pore size, and the chemical and physical stability of the polymer. These factors can be controlled by changing the degree of the cross-linking of the polymer and the conditions employed during the polymerization.

There are three main types of polymers associated with polymer supported reagents:

- 1) microporous or gel type resins
- 2) macroporous resins
- 3) macroreticular resins

Microporous resins are prepared from a vinyl monomer and a difunctional vinyl comonomer in the absence of any solvating medium. In the dry state they are microporous and on contact with a good solvent a soft gel network is formed and porosity is generated depending on the degree of copolymerization. In practice, resins of 2% cross-link have found very wide application.

Macroporous polymers are prepared as above with the inclusion of an inert solvent. The solvent solvates both monomer and polymer and a polymer network is thus formed with a considerable degree of porosity. Removal of the solvent causes a reversible collapse of the polymer network.

The solvent employed during the polymerization is a good solvent for the monomer but is a precipitant for the polymer and generates macroreticular polymers. These polymers are highly porous and rigid and retain their volume and shape when the solvent is removed.

The role of a solvent in the use of a polymer supported reaction is critical. It should interact with the polymer network for the maximum diffusional mobility of reagent molecules and also should have the correct solvating characteristics for any chemical transformations to be carried out.

#### **OXIDATION**

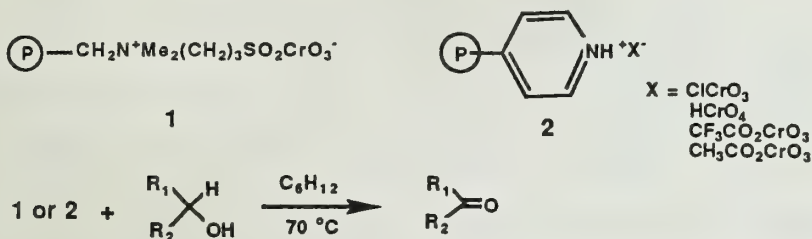
Oxidation of alcohols is achieved by many reagents. When Cr(IV) derivatives are used the work-up of the reaction mixture is sometimes complicated. Chromium trioxide is the widely used starting material to prepare chromium complexed nitrogen heterocycles to make neutral and acidic oxidizing reagents. All these reagents suffer several drawbacks, one of which



is tedious recovery of the product from the chromium oxides byproducts. In order to overcome these problems the use of several polymer supported chromium reagents has been reported recently.<sup>2</sup> Two such reagents are polymer supported quaternary ammonium complex chromates (1) and polymer supported acidic ammonium complex chromates (2).

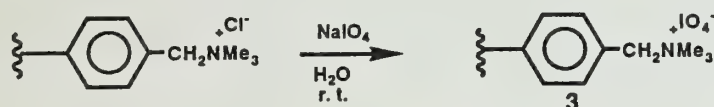
These new reagents were found to be more effective oxidants for alcohols, with comparable or improved yields of products, relative to the unsupported reagents (Scheme II).

Scheme II



The periodate anion oxidizes various functional groups. However, these salts can generally be used only in hydroxylic media. A recent report of the use of polymer supported quaternary ammonium periodate resins (3) is a practical alternative (Scheme III).<sup>3</sup>

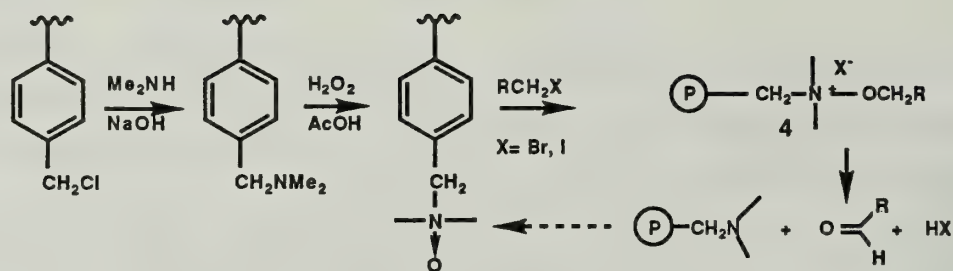
Scheme III



This reagent can be used in a range of solvents, including aprotic solvents, to oxidize various quinols, catechols, hydroazobenzenes, triphenylphosphines, sulfides, etc, and to cleave 1,2 diols.

The use of a new polymer supported reagent based on a cross-linked polystyrene matrix modified to incorporate a tertiary amine oxide residue (4) has been reported recently.<sup>4</sup> This reagent can be used to oxidize primary alkyl halides and benzylic halides into aldehydes. In all cases the yields were excellent and no overoxidation to form carboxylic acids was observed. This reagent can be used to oxidize secondary halides to the corresponding ketones, but alkene formation was observed as a side reaction. As expected, isolation involved filtration and evaporation of solvent to obtain the desired products. The polymeric byproduct can be regenerated by treatment with hydrogen peroxide (Scheme IV).

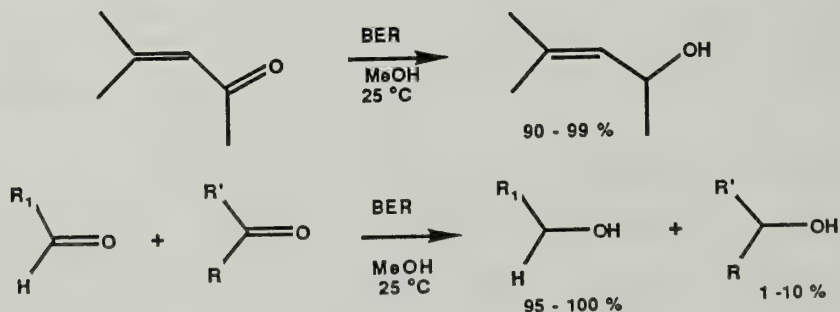
Scheme IV



## REDUCTION

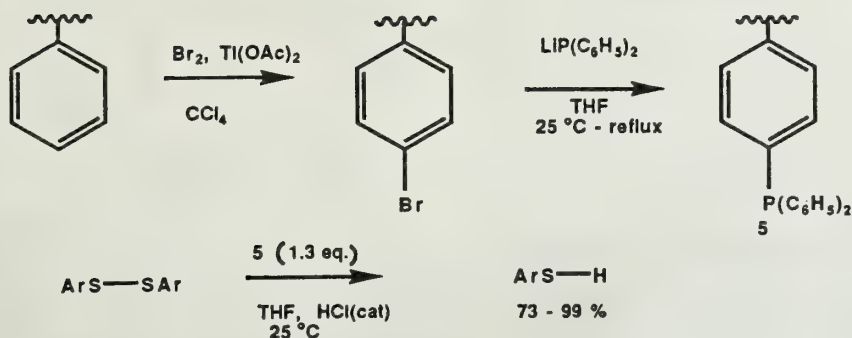
Selective reduction of one carbonyl group in the presence of another one is a frequent synthetic problem. Borohydride exchange resins have been used to overcome this problem.<sup>5</sup> The chemoselectivity was studied by competitively reducing equimolar mixtures of aldehydes and ketones with borohydride exchange resin (BER) reagent. This study has shown that BER has very good selectivity between aldehydes and ketones with preferential reduction of aldehydes in ethanol at 25 °C. This selectivity is equal to or greater than that of previously reported selective reagents. The BER exhibited a high selectivity in the reduction of  $\alpha,\beta$ -unsaturated aldehydes and ketones to corresponding unsaturated alcohols in high yields (Scheme V).<sup>6</sup> Besides this chemoselectivity, BER has significant advantages over other hydride systems. The simple separation of BER reagent by filtration gives the product free from boron product and the polymeric reagent can be regenerated simply by treating with sodium borohydride solution.

Scheme V



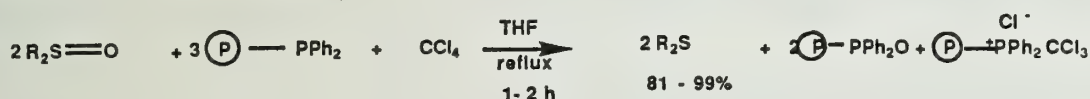
The selective cleavage of disulfides has been accomplished by using a polymer supported phosphine reagent (5).<sup>7</sup> The treatment of a disulfide in THF with polymeric phosphine reagent followed by filtration produced excellent yields of the desired thiols (Scheme VI).

Scheme VI



The use of polystyryldiphenylphosphine with carbon tetrachloride provides a very effective means of reducing sulfoxides to sulfides (Scheme VII).<sup>8</sup> The reaction provides high yields, mild reaction conditions, a broader tolerance for functional groups, and a convenient isolation procedure.

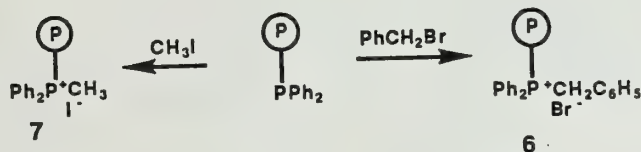
Scheme VII



## CONDENSATION

The Wittig reaction is one of the most valuable reactions in synthetic organic chemistry for the regiospecific introduction of a carbon-carbon double bond. Insoluble phosphines (6 and 7) have been prepared using divinylbenzene cross-linked polystyrene (Scheme VIII).<sup>9</sup> Phosphoranes were generated using an alkoxide and subsequent treatment with a variety of carbonyl compounds provided alkenes in 52-96% yield depending upon the extent of cross-linking.

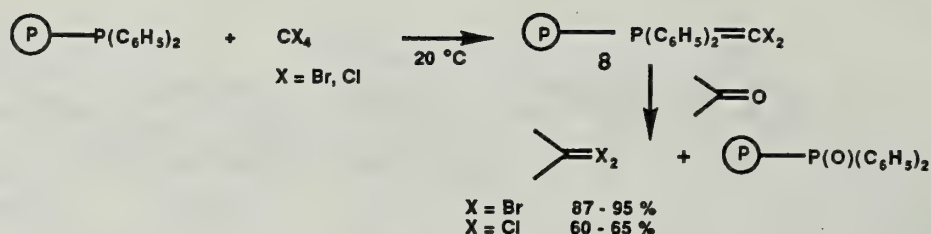
Scheme VIII



The results show the quality of the reaction and its very easy workup, involving simple filtration. The byproduct polymeric phosphine oxides are reduced to phosphines and reused for Wittig reactions with no reduction in yield.

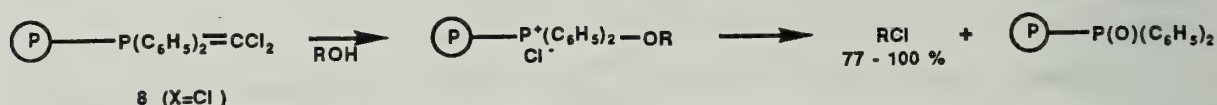
Dihalo-olefins were prepared by treating carbonyl compounds with polymer supported phosphines and with carbon tetrachloride, carbon tetrabromide, or

Scheme IX



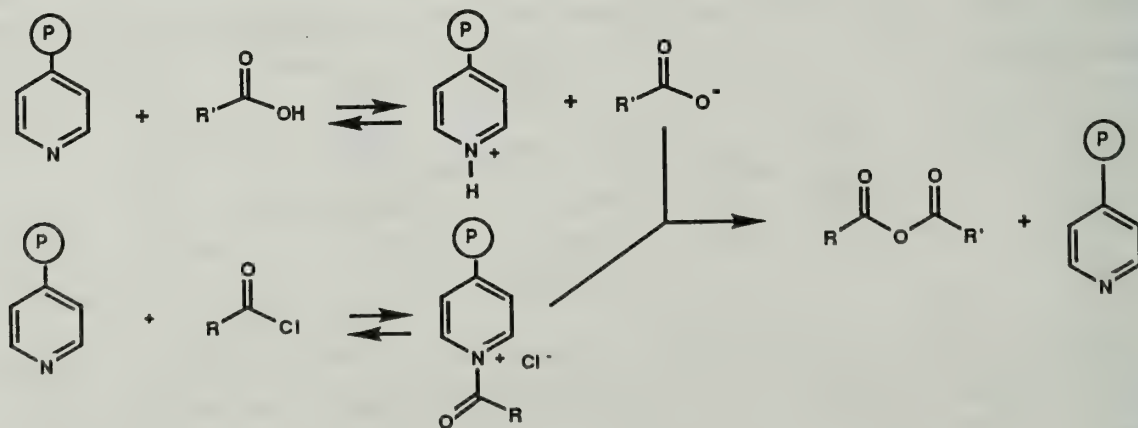
bromotrichloromethane (Scheme IX).<sup>10</sup> The triphenylphosphine-carbon tetrachloride reagent can be used for chlorination, condensation, and dehydration reactions. The use of polymer supported phosphine- $\text{CCl}_4$  (8 X = Cl) reagent was used to convert alcohols and thiols into alkyl chlorides and acids into acid chlorides and amides (Scheme X).<sup>11</sup> This polymer supported reaction is faster than the soluble phosphine reaction.

Scheme X



High yields of asymmetric and symmetric acid anhydrides are produced by using carboxylic acids in the presence of a solid state copolymer of 4-vinylpyridine (P4-VP). In the case of mixed anhydride formation, an equimolar quantity of an acid chloride is treated with a carboxylic acid in dichloromethane in the presence of polymeric 4-vinylpyridine (Scheme XI).<sup>12</sup> The yields of the desired mixed anhydrides are generally > 90%.

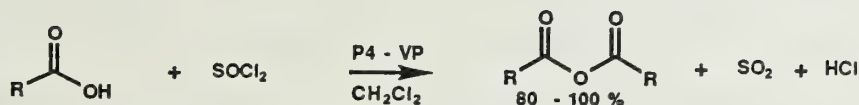
Scheme XI



High yields of symmetric anhydrides are produced by treating a mixture of a carboxylic acid and one half equivalent of thionyl chloride in dichloromethane with a solid copolymer of 4-vinylpyridine (Scheme XII).<sup>13</sup>



## Scheme XII



## ASYMMETRIC SYNTHESSES

Although a large number of asymmetric reactions have been developed for the preparation of chiral substances, only a few reactions are truly catalytic in nature. The main disadvantages in stoichiometric asymmetric syntheses are that many chiral reagents are expensive and their quantitative recovery is not always possible and in many reactions the chiral reagent is similar to the product. Therefore, tedious separation procedures may be required.

Both these problems can be solved using polymer supported chiral reagents. This will ensure easy recovery of chiral reagent and will leave the desired product in the soluble phase.

Polymer bound (1*R*, 2*S*)-(-)-ephedrine (10) is a useful regenerable chiral auxiliary, which can be used as a complex of lithium aluminum hydride and an added achiral alcohol in the enantioselective reduction of carbonyl compounds (Scheme XIII).<sup>14</sup> Reduction of acetophenone with lightly loaded (degree of functionalization-DF = 0.09) polymer bound hydride reagent in ether at -15 °C gives the desired alcohol in 93% yield (76% ee).

## Scheme XIII

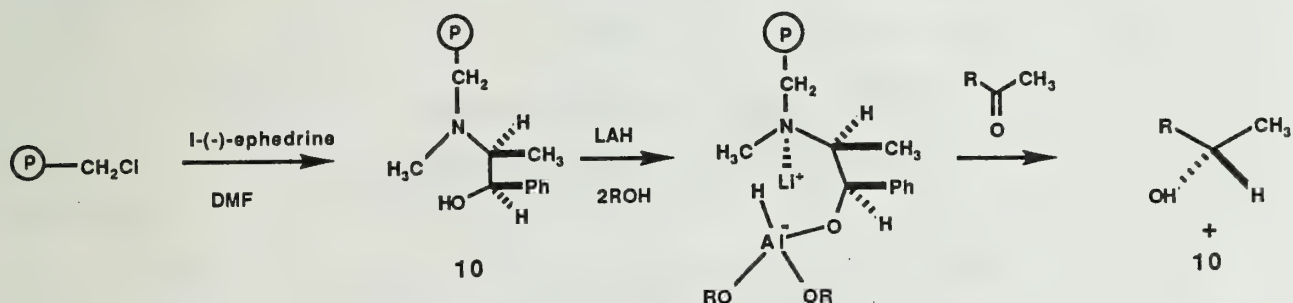


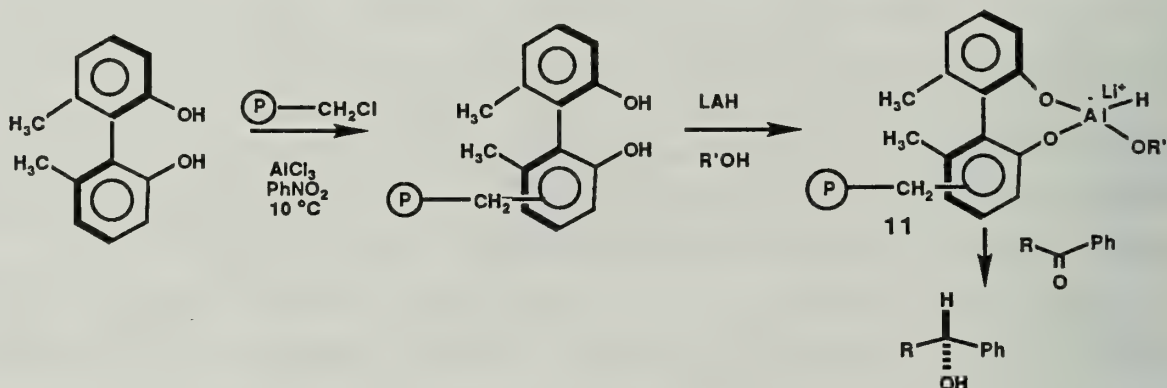
Table 1. Reduction of acetophenone

	molar ratio LAH / P / ROH	solvent	T °C	reaction cycle	yield %	ee %
1	1 : 1 : 2	ether	-15	1	93	76
2	1 : 1 : 2	ether	-15	2	97	79
3	1 : 1 : 2	ether	-15	5	94	79
4	1 : 1 : 2	ether	0	1	98	71

These results showed the ability of the reagent to be recycled and reused (Table I). It was generally observed that the first reaction cycle afforded a slightly lower enantioselectivity than subsequent cycles.

Reduction of alkyl phenyl ketones with lithium aluminum hydride complexes containing a chiral dihydroxybiphenyl bound to a polymeric reagent (11) showed high enantioselectivity (Scheme XIV).<sup>15</sup>

#### Scheme XIV



Polymer supported chiral reagents have been prepared from (*S*)-prolinol and borane and used in enantioselective reduction of a series of prochiral ketones.<sup>16</sup> These reagents (12) are known to give reasonably good yields of alcohols (Table II). In some cases, optical purity of the product alcohol is greater than that produced by the use of corresponding soluble reagents.

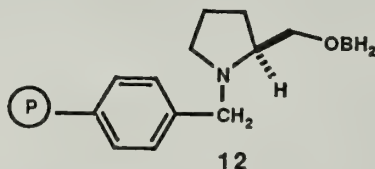


Table II. Reduction of Phenyl Propyl ketone using 12

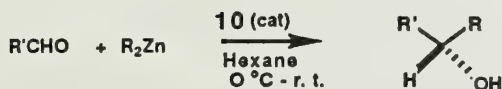
Degree of cross-link %	Yield %	ee %
1	94	75
2	96	72
20	95	58

The polymer bound reagents used could be conveniently separated and recycled after treatment with borane. The results show that both optical and chemical yields were reproducible when re-used.

The catalytic asymmetric alkylation of carbonyl compounds is a potentially important method for the preparation of enantiomerically pure alcohols. Polymer bound ephedrine (11) is an efficient catalyst for

enantioselective addition of dialkylzinc to aldehydes (Scheme XV).<sup>17</sup> The catalyst was removed by filtration and recovered in >95% yield after alkaline treatment.

#### Scheme XV



The use of several polymeric amino alcohols in the addition of diethylzinc to benzaldehyde has been reported recently.<sup>18</sup> The best results were obtained (Table III) using a polymeric catalyst derived from *N,N*-dialkylated(-)-3-aminoisoborneol (**14**). This study shows clearly that the chiral alkoxide produced by the reaction is not bound covalently to the initially formed polymeric zinc complex. The alkyl transfer occurs from the excess free dialkylzinc in the solution.

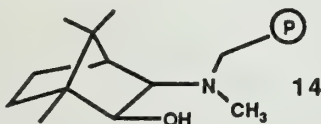


Table III. Alkylation using **14**

Aldehyde	Yield %	ee %
<b>1</b> Benzaldehyde	91	92
<b>2</b> <i>o</i> -Methoxybenzaldehyde	88	93
<b>3</b> <i>o</i> -Ethoxybenzaldehyde	92	95

Recently Frechet reported a cross-linked polymer containing pendant (*R*)- $\alpha$ -methylbenzylamine units and used it in the enantioselective alkylation of cyclohexanone.<sup>19</sup> The optical purity was much higher than that obtained using unsupported reagents. The increased enantioselectivity of the polymer supported reaction is probably due to a decrease in the conformational mobility of the polymer bound intermediate.

#### CONCLUSION

The most important advantage in using a functionalized polymer as a reagent or catalyst is the simplification of product workup, separation, and isolation. Supported reagents may also be conveniently used in excess to drive reactions to completion. Since these reagents are regenerable, expensive reagents can be used efficiently. There are some disadvantages associated with these reagents, the most important being the additional time and cost involved in synthesizing a supported reagent.

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# 1,3-DIPOLAR CYCLOADDITIONS OF AZOMETHINE YLIDES GENERATED VIA DESILYLATION METHODOLOGY

Reported by Gary P. Lutz

18 April 1988

## INTRODUCTION

The 1,3-dipolar cycloaddition reaction represents one of the best ways of generating five-membered heterocyclic ring systems. The popularity of this cycloaddition is partly due to the ease with which cycloaddition takes place, the flexibility with which multiple functional groups can be introduced at various positions, good stereochemical control, and fair predictability of its regiochemistry. Since pyrrolidine and pyrrole heterocyclic ring systems are commonly encountered in natural products, simple and versatile routes to these systems are of synthetic interest. One of the most direct routes to pyrrolidine and pyrrole skeletons is via the 1,3-dipolar cycloaddition of azomethine ylides with suitable olefins and alkynes.<sup>1</sup> There are several methods for generating azomethine ylides from various starting materials. A few representative methods are thermal and photolytic ring opening of aziridines,<sup>2</sup> deprotonation of immonium salts,<sup>2,3</sup> decarboxylative condensation of  $\alpha$ -amino acid derivatives with carbonyl compounds,<sup>4a,b</sup> condensation of *N*-substituted  $\alpha$ -amino acid esters with carbonyl compounds followed by loss of water,<sup>4a,c</sup> and a variety of desilylation methods. Several desilylation methods recently used to generate azomethine ylides are the subject of this report.

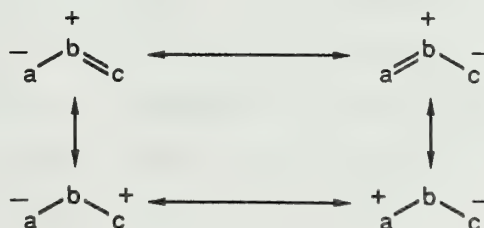
## BACKGROUND AND MECHANISTIC CONSIDERATIONS

According to Huisgen a 1,3-dipole is a species which can be represented by zwitterionic octet structures and which undergoes 1,3-cycloaddition reactions with a multiple bond system, the dipolarophile.<sup>2</sup> The overall system can be regarded as a *heteroallyl anion* which bears no net charge because the central position is occupied by an onium center which balances the negative charge (Scheme I).<sup>2</sup> An important distinction between the 1,3-dipole and the allyl anion can be seen by examining the sextet structures. These resonance struc-

### Scheme I

OCTET STRUCTURES

SEXTET STRUCTURES

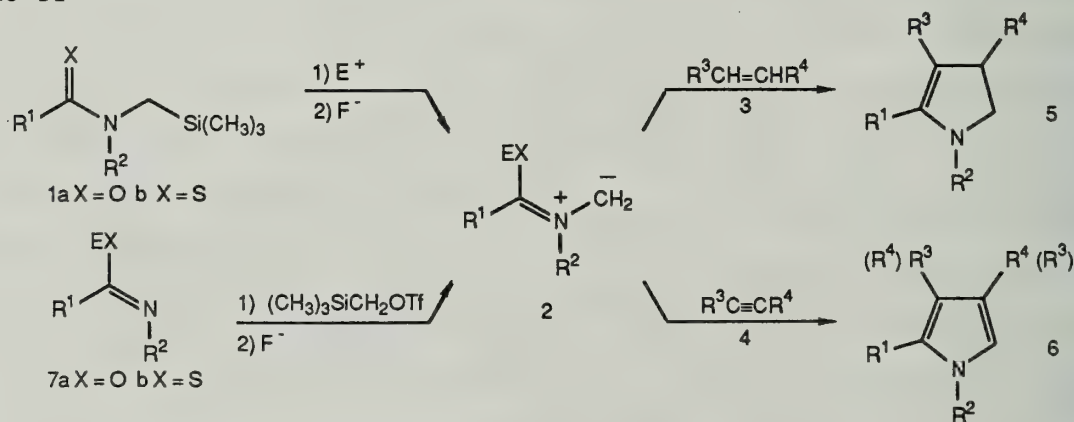


tures show that, unlike the allyl anion, the terminal positions of a 1,3-dipole can be both nucleophilic and electrophilic, and this ambivalence is important in understanding the reactivity of the 1,3-dipole.<sup>2</sup> The bulk of evidence concerning the mechanism of 1,3-dipolar cycloadditions favors a concerted  $[4\pi s + 2\pi s]$  mechanism in accordance with orbital symmetry considerations.<sup>2</sup> In terms of synthetic utility 1,3-dipolar cycloadditions of azomethine ylides are generally stereospecific with respect to both dipole and dipolarophile, show a preference for endo addition, analogous to the Diels-Alder reaction, and have good regioselectivity.<sup>2</sup>

#### DESILYLATION OF IMIDATES OR THIOIMIDATES

One of the first desilylation methods investigated for azomethine ylide generation was the reaction of *N*-(trimethylsilylmethyl) amides or thioamides with various alkylating agents followed by desilylation in the presence of a dipolarophile (Scheme II).<sup>1,5</sup> Since the ylide **2** generated in this manner still

**Scheme II**

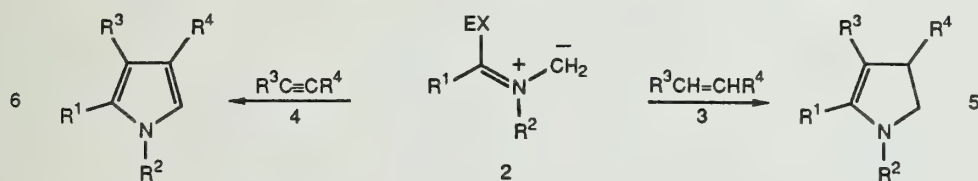


possesses a leaving group, this method provides a good route to both substituted pyrrolines, **5**, and pyrroles, **6**. The immonium ion, first generated by treating **1** with alkylating agents such as methyl trifluoromethanesulfonate or Meerwein's reagent, aids in the desilylation because of the stabilization provided by the adjacent positive charge. Fluoride ion is generally used to achieve desilylation in these reactions, but use of other reagents will be seen with other methods. Vedejs found that replacing the oxygen with sulfur in amide **1a** gave almost a twofold yield increase of cycloadducts, (**5**).<sup>5</sup> The reasons for improved yields are related to the relative ease of thioamide alkylation and greater stability of the thioimide salts being formed.<sup>5</sup> Cycloaddition of ylide **2** with unsymmetrical olefins was found to give good regioselectivity, but cycloaddition of **2** with unsymmetrical alkynes gave

varying mixtures of isomeric pyrroles (6).<sup>5</sup> This loss of regioselectivity has also been seen in other 1,3-dipoles and has been explained for reaction of phenyl azide with phenyl acetylene by the use of Frontier Orbital (FO) theory.<sup>6</sup> Since acetylenes have a lower-energy HOMO and a different HOMO-LUMO gap than a corresponding olefin, cycloaddition is not always restricted to interaction of the LUMO of the dipolarophile with the HOMO of the dipole but can also take place through the HOMO of the dipolarophile with the LUMO of the dipole.<sup>6</sup> Since the HOMO-LUMO gap is similar in energy for the two cases, and the two show opposite regioselectivity, a mixture of isomers is obtained.

The same intermediate ylide 2 can also be generated by treating an *N*-substituted imidate (7a) or thioimide (7b) with trimethylsilylmethyl triflate followed by treatment with fluoride ion.<sup>1</sup> This method also shows a substantial increase in yield when thioimide 7b is substituted for imidate 7a. The greater stability of the thioimide salts may be part of the explanation, but the nucleophilicity of nitrogen's lone pair of electrons may be important. Since sulfur stabilizes the thioimide salt, it may make the nitrogen more nucleophilic. The results for cycloadditions involving ylide 2 are summarized in Table I.

**Table I. Cycloadditions Using Ylide 2 as the 1,3-Dipole**



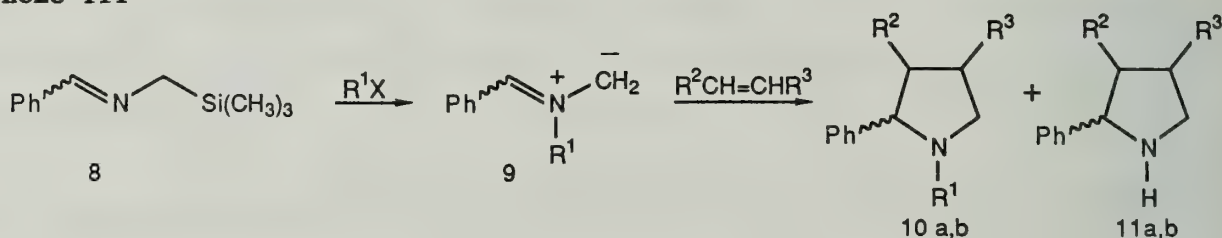
STARTING MATERIAL				DIPOLAROPHILE			PRODUCT			
TYPE	X	R <sup>1</sup>	R <sup>2</sup>	TYPE	R <sup>3</sup>	R <sup>4</sup>	TYPE	R <sup>3</sup>	R <sup>4</sup>	% YIELD
1	O	-(CH <sub>2</sub> ) <sub>3</sub> -		3	CO <sub>2</sub> CH <sub>3</sub>	H	5	CO <sub>2</sub> CH <sub>3</sub>	H	37
1	S	-(CH <sub>2</sub> ) <sub>3</sub> -		3	CO <sub>2</sub> CH <sub>3</sub>	H	5	CO <sub>2</sub> CH <sub>3</sub>	H	66
1	S	-(CH <sub>2</sub> ) <sub>4</sub> -		4	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	6	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	66
1	S	-(CH <sub>2</sub> ) <sub>4</sub> -		4	$\begin{Bmatrix} \text{CO}_2\text{CH}_3 & \text{H} \\ \text{H} & \text{CO}_2\text{CH}_3 \end{Bmatrix}$		6	$\begin{Bmatrix} \text{CO}_2\text{CH}_3 & \text{H} \\ \text{H} & \text{CO}_2\text{CH}_3 \end{Bmatrix}$		31 25
7	O	Ph	CH <sub>3</sub>	4	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	6	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	48
7	S	Ph	CH <sub>3</sub>	4	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	6	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	74
1	O	Ph	CH <sub>2</sub> Ph	3	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	5	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	39
1	O	Ph	CH <sub>2</sub> Ph	4	$\begin{Bmatrix} \text{CO}_2\text{CH}_3 & \text{H} \\ \text{H} & \text{CO}_2\text{CH}_3 \end{Bmatrix}$		6	$\begin{Bmatrix} \text{CO}_2\text{CH}_3 & \text{H} \\ \text{H} & \text{CO}_2\text{CH}_3 \end{Bmatrix}$		32 16



## FORMATION OF IMMONIUM SALTS FOLLOWED BY DESILYLATION

A second major desilylation approach to the azomethine ylides involves the reaction of a suitable imine with electrophiles to generate an immonium salt which is then desilylated to afford the ylide **9** which can undergo cycloaddition reactions with olefins and alkynes (Scheme III).<sup>7</sup> In these reactions desilylation can be accomplished with only the alkyl halide being added<sup>7a,b</sup> and may be the result of spontaneous loss of trimethylsilyl halide from the intermediate imidate salt, or another halide ion may assist in removal of the trimethylsilyl group from the imidate salt. Desilylation can also be accomplished with a catalytic mixture of trimethylsilyl triflate and cesium fluoride,<sup>7c</sup> with catalytic amounts of trifluoroacetic acid,<sup>7d,e</sup> or with one equivalent each of water and acetic acid.<sup>7f</sup> Since there is no leaving group present in the ylide **9**, cycloaddition with olefins gives pyrrolidines and cycloaddition with alkynes gives 3-pyrrolines; the latter can easily be converted to pyrroles by oxidation.

## Scheme III



Depending upon the actual reagents involved, this reaction will produce either *N*-substituted (**10**) or *N*-unsubstituted (**11**) pyrrolidine ring systems. When butyl halides were used as electrophiles, reaction of ylide **9** with dimethyl fumarate led to mixtures of **10** and **11**, and the ratio of **10** to **11** was dependent upon the halide used.<sup>7a,b</sup> These results are summarized in Table II. Reaction was slower as the butyl halide was changed from iodide to chloride, and yields also decreased.<sup>7a</sup> The proposed mechanism for this reaction involves reaction of **8** with trimethylsilyl halide - generated in situ - to give ylide **9**.

Table II. Cycloaddition of Imine **8** with Various Alkyl Halides

R <sup>1</sup> X	TOTAL YIELD*	% 10a,b	% 11a,b
BuI	100	99	1
BuBr	100	63	37
BuCl	66	—	100
BuOTs	79	50	50

\* Dimethyl fumarate was used as the dipolarophile for all reactions.



where  $R^1$  is trimethylsilyl, and this ylide then undergoes cycloaddition to give, initially an *N*-trimethylsilyl pyrrolidine, but the latter is hydrolyzed upon work-up to the *N*-unsubstituted pyrrolidine 11.<sup>7a,b</sup> Support for this mechanism has been obtained by treating the imine 8 with iodotrimethylsilane in the presence of a dipolarophile followed by work-up with water to give 11 or followed by addition of iodobutane to give the *N*-butyl pyrrolidine 10.<sup>7b</sup> Further support for the *N*-trimethylsilyl substituted ylide (9) being the reactive species comes from the fact that a mixture of trimethylsilyl triflate and cesium fluoride can be used catalytically for the cycloaddition of 8 with dipolarophiles to give the *N*-unsubstituted product 11.<sup>7c</sup>

Regioselectivity in cycloaddition with unsymmetrical olefins of the ylide generated from imine 8, by either alkylation or silylation, favors the product where the olefin's carbon bearing the electron withdrawing group becomes bonded to the substituted carbon of the 1,3-dipole even though this product is usually the more sterically hindered product of the two possible regioisomers. There are also two new stereocenters present in the pyrrolidines 10 and 11 that are not present in the pyrrolines 5, and while the dipolarophile's substituents retain their relative stereochemistry, stereoselectivity with respect to the 1,3-dipole appears to be poor. Results for cycloaddition of the ylide 9 with various olefins are summarized in Table III. This apparent lack of stereoselectivity may be due to rotation about the bond between nitrogen and the substituted carbon in the ylide or to a lack of stereoselectivity in generating the original imine double bond. Since the stereochemistry of the

**Table III. Stereoselectivity of Cycloadditions of Ylide 9**

ELECTROPHILE	DIPOLAROPHILE			PRODUCT (a : b) <sup>*</sup>		YIELD (%)
	R <sup>2</sup>	R <sup>3</sup>		10 a	10 b	
Bul	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	( <i>trans</i> )	3	2	82
Bul	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	( <i>cis</i> )	1	2	61
Bul	CO <sub>2</sub> CH <sub>3</sub>	H		3	2	45
PhCH <sub>2</sub> Br	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	( <i>trans</i> )	1.2	1	79
				11a : 11b		
(CH <sub>3</sub> ) <sub>3</sub> SiOSO <sub>2</sub> CF <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	( <i>trans</i> )	5	4	91
(CH <sub>3</sub> ) <sub>3</sub> SiOSO <sub>2</sub> CF <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	( <i>cis</i> )	2	3	83
(CH <sub>3</sub> ) <sub>3</sub> SiOSO <sub>2</sub> CF <sub>3</sub>	CON(CH <sub>3</sub> )CO			1	2	85
(CH <sub>3</sub> ) <sub>3</sub> SiOSO <sub>2</sub> CF <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	H		5	4	83

\* a has R<sup>2</sup> *cis* to Ph; b has R<sup>2</sup> *trans* to Ph; R<sup>2</sup> and R<sup>3</sup> retain their relative stereochemistry.

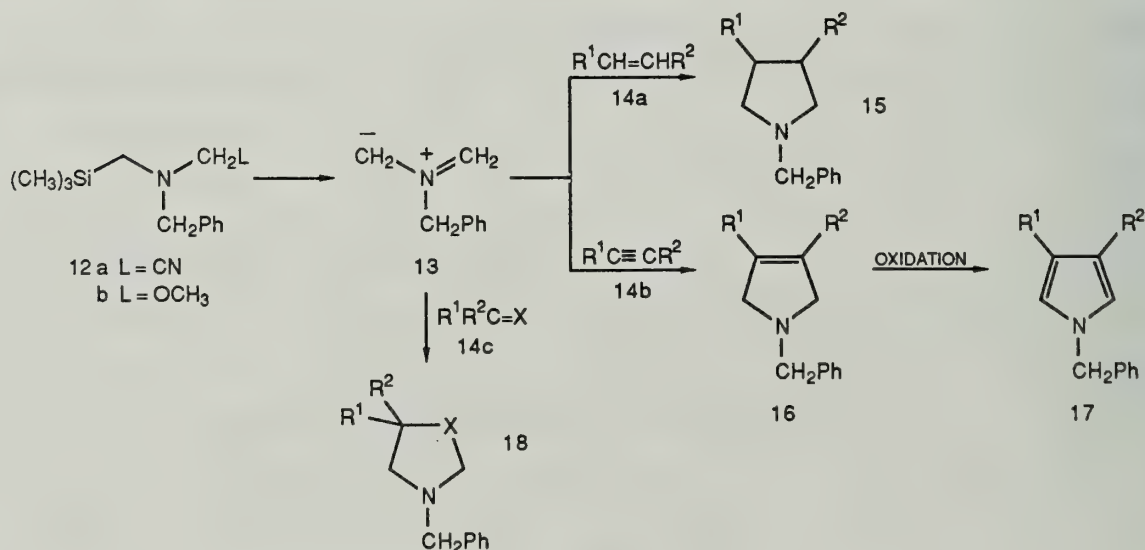
starting imines is not reported, it is difficult to judge which effect, if either, may be involved.

If the phenyl group of imine **8** is replaced by an ester group, ylides generated from this species will undergo cycloaddition reactions with olefins to give various proline derivatives. Regioselectivity of this reaction was found to be poor,<sup>7d,e</sup> but these reactions were usually preformed with unsymmetrical, disubstituted alkenes like methyl cinnamate. The coefficients of this dipolarophile may not be different enough to give good regioselectivity. Also, the ester group of the dipole may have a similar effect on the dipole.

#### ELIMINATION OF A LEAVING GROUP FROM AN AMINE PRIOR TO DESILYLATION

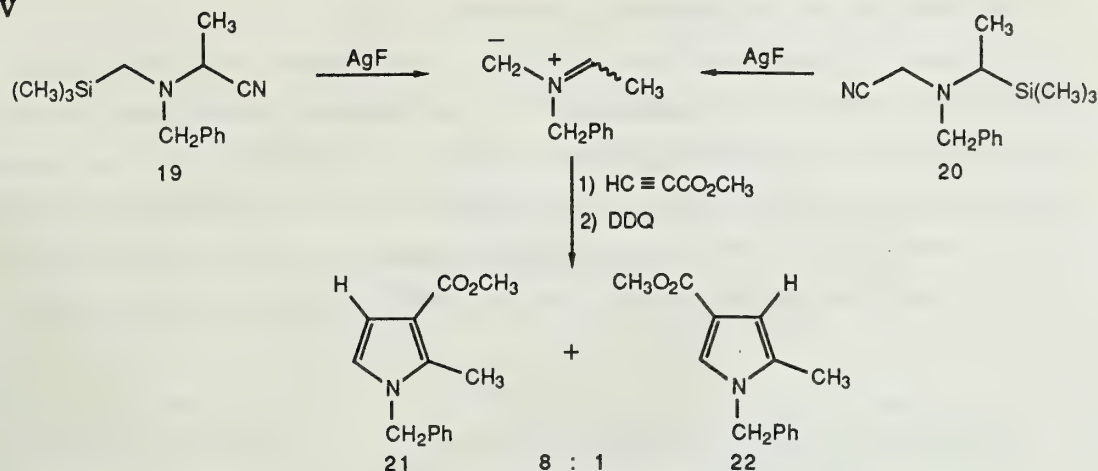
A third general method used for generating azomethine ylides via desilylation involves the elimination of a leaving group from an amine to form an iminium salt prior to desilylation (Scheme IV). This procedure can be used to synthesize pyrrolidines, 3-pyrrolines, pyrroles, oxazolidines, and thiazolidines depending upon the dipolarophiles used.<sup>8</sup>

Scheme IV



Silver fluoride is usually used to generate ylide **13** when the  $\alpha$ -cyanotrimethylsilylamine **12a** is used in these cycloadditions.<sup>8a,b</sup> This reaction is believed to proceed via a metal assisted removal of cyanide ion followed by fluoride ion desilylation.<sup>8a</sup> Evidence for the existence of the ylide intermediate has come from cycloadditions of the isomeric  $\alpha$ -cyanotrimethylsilylamines **19** and **20** (Scheme V). Cycloaddition of **19** or **20** with methyl propiolate followed by oxidation of the intermediate 3-pyrrolines to the corresponding pyrroles gave the same ratio of isomers **21** and **22**.<sup>8a</sup>

Scheme V



Ylide 13 can be generated from the methoxy amine 12b with fluoride salts (alone<sup>8c,d</sup> or in combination with trimethylsilyl triflate<sup>8e</sup>) or with catalytic amounts of trifluoroacetic acid.<sup>8d,f</sup> The mechanism of this reaction has been termed 1,3-elimination of methoxytrimethylsilane<sup>8e</sup>, but the specifics of the mechanism have not been examined. The results of the cycloadditions of 12a and 12b are summarized in Table IV.

Table IV. Cycloadditions of Ylide 13 Using Various Desilylating Agents

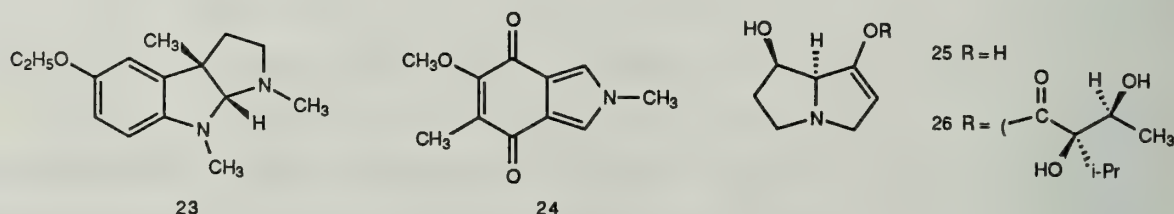
STARTING MATERIAL	DESILYLATING AGENT	DIPOLAROPHILE			PRODUCT	
TYPE		TYPE	R <sup>1</sup>	R <sup>2</sup>	TYPE	% YIELD
12a	AgF	14a	Ph	COCH <sub>3</sub> ( <i>trans</i> )	15	55
12a	AgF	14a	Ph	CO <sub>2</sub> CH <sub>3</sub> ( <i>trans</i> )	15	63
12a	AgF	14b	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	17	62
12a	AgF	14b	H	CO <sub>2</sub> CH <sub>3</sub>	17	65
12b	CF <sub>3</sub> CO <sub>2</sub> H	14a	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub> ( <i>cis</i> )	15	94
12b	CF <sub>3</sub> CO <sub>2</sub> H	14a	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub> ( <i>trans</i> )	15	97
12b	Bu <sub>4</sub> NF	14a	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub> ( <i>trans</i> )	15	35
12b	(CH <sub>3</sub> ) <sub>3</sub> SiOTf	14a	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub> ( <i>trans</i> )	15	74
12b	CsF/(CH <sub>3</sub> ) <sub>3</sub> SiOTf	14a	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub> ( <i>trans</i> )	15	83
12b	CsF/(CH <sub>3</sub> ) <sub>3</sub> SiOTf	14a	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub> ( <i>cis</i> )	15	83
12b	CF <sub>3</sub> CO <sub>2</sub> H	14a	Ph	CO <sub>2</sub> CH <sub>3</sub> ( <i>trans</i> )	15	87
12b	CF <sub>3</sub> CO <sub>2</sub> H	14b	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	16	66
12b	CF <sub>3</sub> CO <sub>2</sub> H	14b	H	CO <sub>2</sub> CH <sub>3</sub>	16	58
12b	LiF	14c	H	Ph X = O	18	80
12b	LiF	14c	CH <sub>3</sub>	CH <sub>3</sub> X = O	18	60
12b	LiF	14c	Ph	Ph X = O	18	40
12b	LiF	14c	Ph	Ph X = S	18	91



## APPLICATIONS IN NATURAL PRODUCT SYNTHESIS

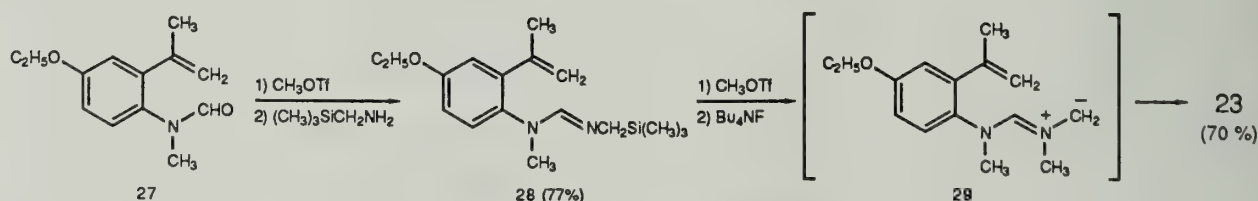
In terms of practical applications, 1,3-dipolar cycloadditions of azomethine ylides generated via desilylation methodology have found use in the synthesis of several substituted heterocyclic compounds. A few representative examples include their use in the synthesis of the neurotoxic physostigmine alkaloid eserethole (23),<sup>9</sup> a *Reniera* isoindole (24),<sup>10</sup> and the pyrrolizidine alkaloids retronecine (25) and indicine (26)<sup>11</sup> as seen in Figure I.

Figure I



The synthesis of eserethole represents an example of an intramolecular cyclization involving an azomethine ylide. Several other intramolecular cyclizations of azomethine ylides have been attempted, but no cyclized products were isolated.<sup>1,8a,c</sup> These reactions usually did not contain an activated olefin,<sup>1,8a</sup> or a different reagent was used to initiate ylide formation.<sup>8c</sup> As can be seen in Scheme VI, the olefin used in the synthesis of eserethole is activated by conjugation with the benzene ring. The cyclization was performed in methylene chloride at room temperature to give a 70% yield of ( $\pm$ )-eserethole from the ylide precursor (28).<sup>9</sup>

Scheme VI



## CONCLUSION

The 1,3-dipolar cycloaddition of azomethine ylides to dipolarophiles is a very useful reaction for the synthesis of five-membered rings containing nitrogen. The desilylation method of azomethine ylide generation and subsequent cycloaddition shares most of the advantages of other methods of generation such as good regioselectivity, mild reaction conditions, and fair to high yields, but the desilylation methods may offer a greater versatility in terms of potential starting materials, actual reaction conditions, poten-



tial for substitution, and availability of some starting materials. On the contrary, there are some problems which have not been solved. One of the major problems is the lack of reactivity of the azomethine ylides with unactivated olefins like cyclohexene. Another is the difficulty of using them in intramolecular cycloadditions.<sup>9a,c</sup> A third problem appears to be controlling stereoselectivity with respect to substituted carbons of the dipole. As these reactions become better understood, their use in organic synthesis should continue to increase.

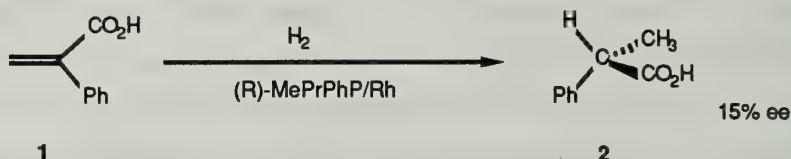
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April 21, 1988

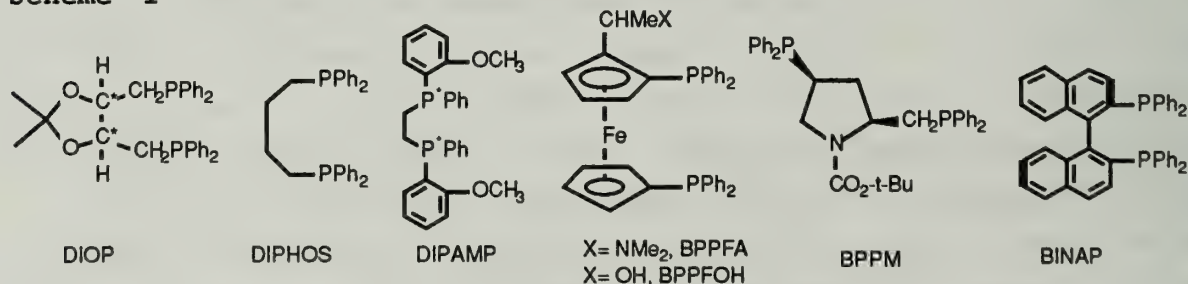
## INTRODUCTION

An important advantage of homogeneous hydrogenation over the usual heterogeneous catalysis methods is high selectivity. This selectivity has been applied effectively in the synthesis of optically active amino acids.<sup>1</sup> The first achiral homogeneous catalyst,  $\text{Rh}(\text{PPh}_3)_3\text{Cl}$ , was used by Wilkinson in 1966 in the hydrogenation of alkenes and alkynes. This complex catalyst was much more reactive than previously used homogeneous catalysts, providing a high yield at room temperature.<sup>2</sup> In 1968, Hornor and Knowles replaced triphenylphosphine with a chiral phosphine and used the catalyst in the synthesis of **2**.<sup>3</sup> Subsequently, Kagan and Dang demonstrated that a chiral

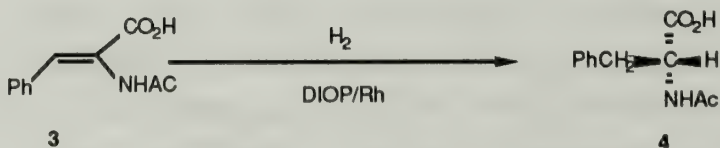


bidentate ligand lacking a chiral phosphorus atom may be used (Scheme I).<sup>4</sup> With DIOP/Rh as catalyst, amino acid **4** was synthesized with an optical yield

### Scheme I



of 70-80%. These results were later improved by using a family of new chiral ligands (e.g., DIPAMP).<sup>5</sup> Furthermore, optical yields approaching 100%



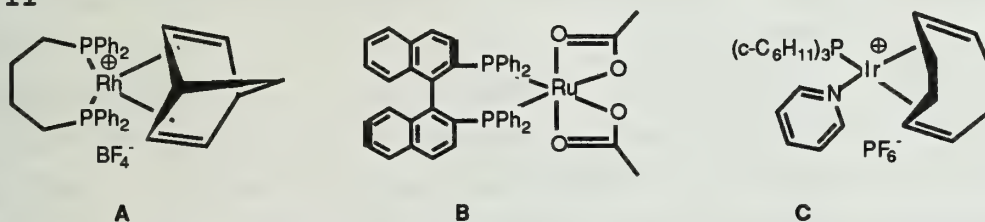
ee were achieved in the hydrogenation of dehydroamino acids to the corresponding amino acids when homogeneous cationic rhodium complexes

containing chiral phosphine ligands were used as catalysts.<sup>6</sup> The commercial synthesis of L-DOPA by asymmetric hydrogenation affords an important practical application of this extraordinarily stereoselective catalysis.<sup>7</sup> This enamide chemistry has been extensively reviewed and will not be covered. The present report is concerned with the asymmetric catalytic hydrogenation of prochiral olefins and ketone derivatives, and hydroxyl-directed hydrogenation.

## CATALYSTS STUDY

As mentioned above, homogeneous catalysts are complexes of transition metals with various phosphorus ligands which are soluble in organic solvents. The metals often used in chiral homogeneous catalyst are rhodium and ruthenium. For the directed hydrogenation of an olefin, cationic rhodium and iridium catalysts are usually used. Three types of catalyst precursors are shown in Scheme II: cationic rhodium complex A,<sup>8a</sup> neutral ruthenium complex B,<sup>8b</sup> and cationic iridium catalyst C.<sup>8c</sup>

Scheme II



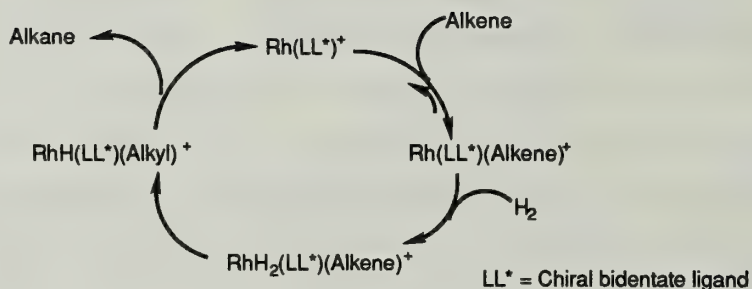
Asymmetric homogeneous hydrogenation using metal complexes depends on the use of chiral ligands. The stereochemical characteristics of the ligand determine the results of the asymmetric reaction. Actually, only a relatively limited combination of catalysts and substrates can give products in high optical yield<sup>1c</sup> and such catalysts usually contain chelating diphosphine ligands. Examples of some of the phosphorus ligands which are used in catalytic hydrogenation of this report are shown in Scheme 1.<sup>9,8b</sup> Chirality of phosphine ligands may result from an asymmetric phosphorus or asymmetric carbon atom or from a chiral axis (e.g., BINAP, BPPFA).

## MECHANISM

A possible general mechanism for Rh(I) asymmetric catalysis is shown in Scheme III.<sup>10</sup> The sequence of reactions involves complexation of the substrate and oxidative addition of hydrogen to rhodium complex. The complex then reacts with hydrogen to give hydrogenated products.



Scheme III

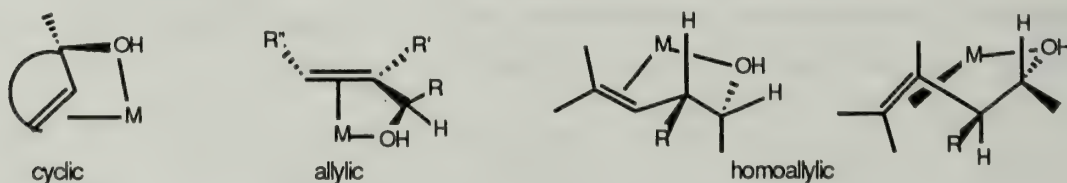


Various studies have demonstrated that high enantioselectivity is obtained if the catalytic complex is tightly bound. Thus, bidentate ligands, especially conformationally restricted ones, are generally the most effective. In addition, prochiral olefins must have a polar neighboring group (e.g., a carbonyl or hydroxyl substituent).<sup>1e</sup> The best solvents used in these reactions are methanol, ethanol, 2-propanol, and their mixtures with water.<sup>1</sup>

The formation of a chelate complex in which the olefin and the carboxylate are bound to the metal is the key step in the reaction cycle.<sup>11</sup> The two hydrogen-transfer steps are known to occur with retention of configuration. Therefore, the net result is *cis* addition to the face of the double bond which is complexed to the metal. In most cases, the reaction rate is accelerated by added base, which enhances the strength of complexation.

In hydroxyl-directed hydrogenation, coordination of the hydroxyl group to the metal has been proposed in the transition state. For cyclic cases, face-selective hydrogenation is observed when the hydroxyl group is bound to rhodium or iridium during hydrogenation of the double bond (Scheme IV). Anti-selectivity is invariably found in acyclic allylic alcohols (Scheme IV). Brown explains this through consideration of the non-bonded interactions in the two diastereomeric chelate complexes.<sup>8a</sup> The precursor of the syn-product is strongly destabilized by a 1,2-interaction between the substituent on the hydroxyl carbon (RCHOH) and the other substituents on the double-bond.<sup>12</sup> For homoallylic alcohols, the stereoselectivity is dependent on the stereochemistry of the position  $\alpha$ -to the double bond (Scheme IV.)<sup>1</sup>

Scheme IV





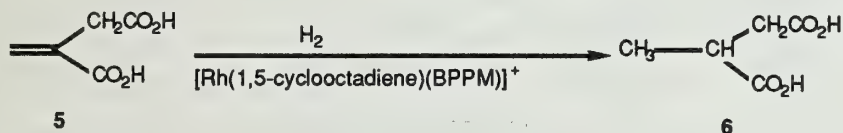
The mechanism of homogeneous hydrogenation of ketones has not been studied in detail. Coordination to form a five or six membered ring complex has been suggested in the transition state.<sup>14</sup>

## APPLICATIONS OF HOMOGENEOUS HYDROGENATION

### Addition to unsaturated acids and derivatives

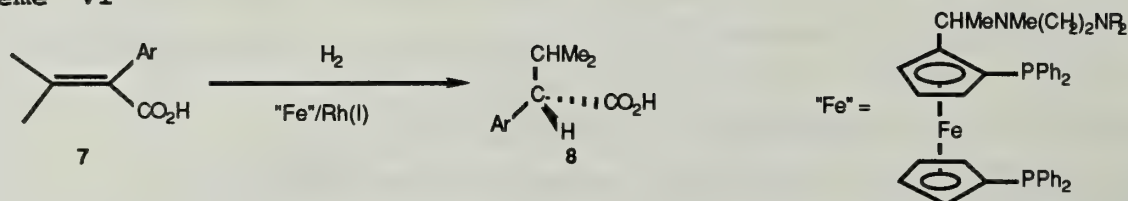
The asymmetric reaction of (*Z*)-acylaminoacrylic acids with rhodium(I) chiral biphosphine complexes has been a major focus in research on homogeneous hydrogenation.<sup>1</sup> Chelation of the acylamino oxygen and the double bond in the metal complex is important. Furthermore, these chelate complexes are rigid, maximizing the substrate-ligand interactions and eventually the enantiofacial discriminating ability of the catalyst.<sup>15</sup> This suggests that good results can be obtained if substituted olefins form a similar type of chelate. In the structurally similar enol esters, Koenig and coworkers have shown that biphosphine ligands which form five-membered chelates work well.<sup>16</sup> By substituting a trifluoromethyl group for the carbonyl, the asymmetric hydrogenation is also efficient. These results demonstrate that it is necessary for prochiral olefins to have a adjacent electron-withdrawing group in order to be hydrogenated efficiently and in high enantiomeric excess. The derivatives of itaconic acid, **5**, are an example of this type of molecule, and Achiwa first reported that the chiral pyrrolidinephosphine-rhodium complexes give optical yields of 93% in the asymmetric hydrogenation of itaconic acid (Scheme V).<sup>17,9b</sup> This is in contrast to *cis*- and *trans*-cinnamic acid which gave low enantioselectivity.<sup>18</sup>

Scheme V



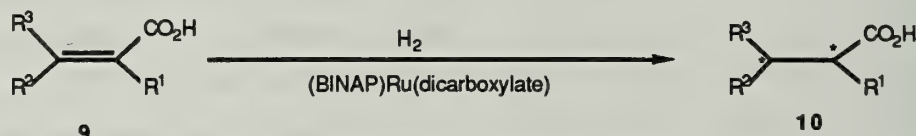
A considerable effort has been made to expand the application of asymmetric hydrogenation to other types of substituted prochiral olefins. Recently, Hayashi, et al., reported that rhodium with chiral (aminoalkyl)-ferrocenylphosphine ligand ("Fe") gave high chemical reactivity and stereoselectivity in the hydrogenation of trisubstituted acids (Scheme VI).<sup>19</sup> In addition, ruthenium(II) complexes with BINAP ligand (See Scheme I)

## Scheme VI



ascatalyst precursors have been used in the stereoselective hydrogenation of a range of substituted acrylic acids lacking the acrylamino moiety (NHCOR) (Scheme VII). The enantioselectivity is affected by hydrogen pressure and the substitution pattern of the olefins. This ruthenium catalyst exhibits a high level of enantio-differentiating ability (>83% ee) in hydrogenation (Scheme VII).<sup>20</sup>

## Scheme VII

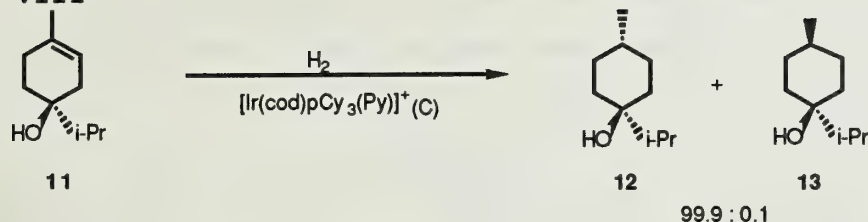


## Hydroxyl-directed homogeneous hydrogenation

In recent years, a great deal of effort has gone into studying the directive effects of the hydroxyl functionality on the stereochemistry of homogeneous hydrogenation. In 1974, Thompson first reported the observation of a directing effect in homogeneous hydrogenation of a tricyclic homoallylic alcohol while using Wilkinson's catalyst.<sup>21</sup> Brown, Stork, Evans and Crabtree all undertook studies in this area in order to develop a general method for stereocontrolled hydrogenation.<sup>22</sup> They demonstrated that some cationic rhodium and iridium phosphine complexes (e.g., [(nbd)Rh(dppb)]PF<sub>6</sub>, [Ir(cod)(pcy<sub>3</sub>)py]PF<sub>6</sub>, and related [(diene)M(dppb)]BF<sub>4</sub> catalysts (M = Rh, Ir)) (See Scheme II) can catalyze diastereoselective hydrogenation of chiral allylic and homoallylic alcohols in which the pre-existing chiral centers induce asymmetry on the prochiral olefins through coordination of the hydroxyl group to the transition metals.

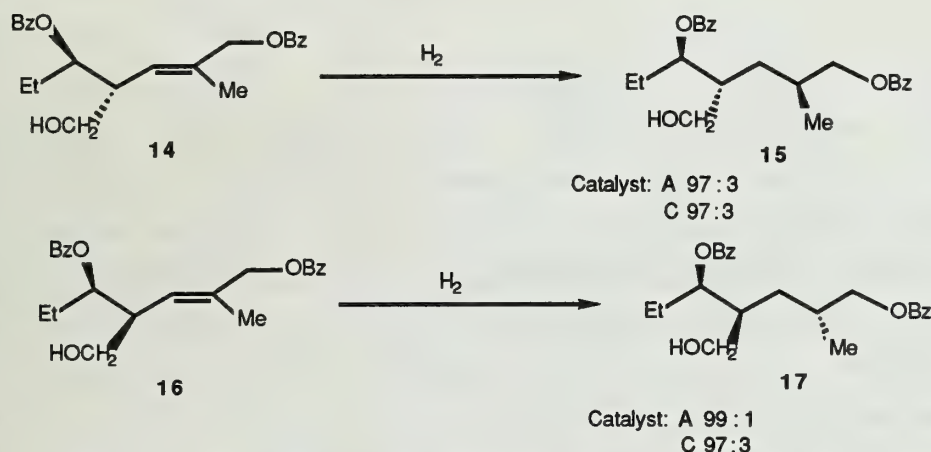
**Hydrogenation of Chiral allylic and homoallylic alcohols.** Cyclic allylic and homoallylic alcohols undergo hydrogenation with high facial-selectivity under hydroxyl-directed hydrogenation (Scheme VIII).<sup>23</sup> Hydrogen addition takes place on the face of the molecule where the OH group is positioned. The Ir catalysts perform better than Rh catalysts in the reductions of hindered double bonds.

Scheme VIII



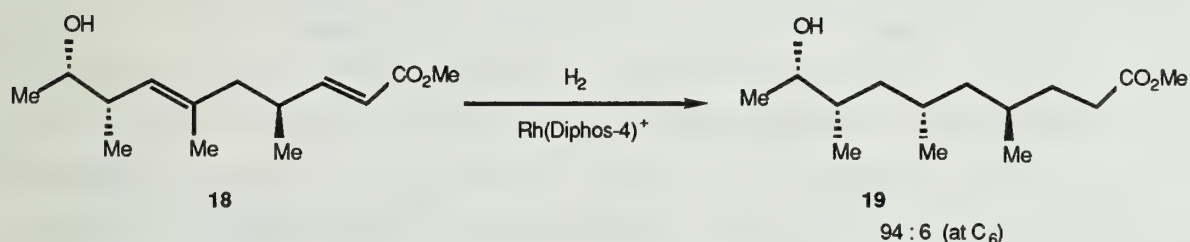
In acyclic allylic and homoallylic alcohols, many reductions can be carried out with high selectivity. Evans and Morrissey showed that acyclic alcohols **14** and **16** can be reduced stereospecifically by using either Ir catalyst (C) or Rh catalyst (A) (see Scheme II). Both catalysts afforded high levels of diastereoselection (Scheme IX).<sup>24</sup>

Scheme IX



This methodology has been used in the synthesis of the fragments of premonensin,<sup>25</sup> and ionomycin.<sup>24</sup> An example illustrating formation of the C<sub>1</sub>-C<sub>10</sub> fragment of ionomycin is shown in Scheme X. Hydrogenation of homoallylic alcohol **18** catalyzed by  $Rh(Diphos-4)^+$  (See Scheme 1) gave the saturated hydroxy ester **19** in 93% yield.

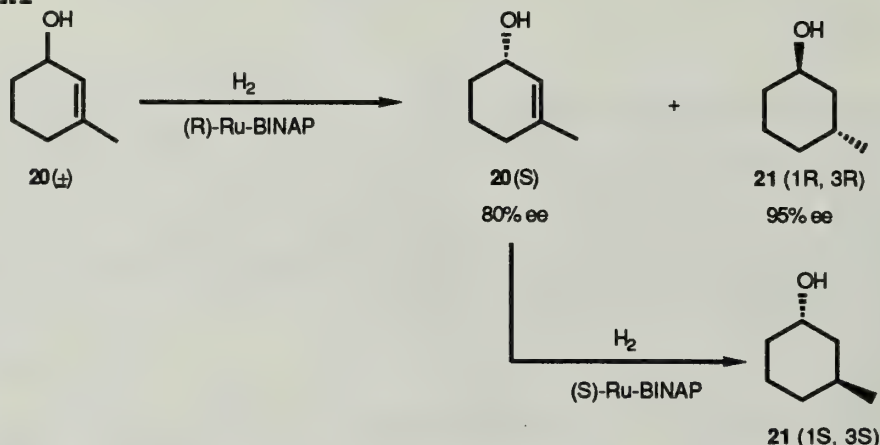
Scheme X



**Hydrogenation of racemic allylic and homoallylic alcohols.** The hydroxyl-directed asymmetric hydrogenation of a racemic allylic alcohol with kinetic resolution was recently reported by Brown and Noyori.<sup>26</sup> When an optically active phosphine-transition metal complex

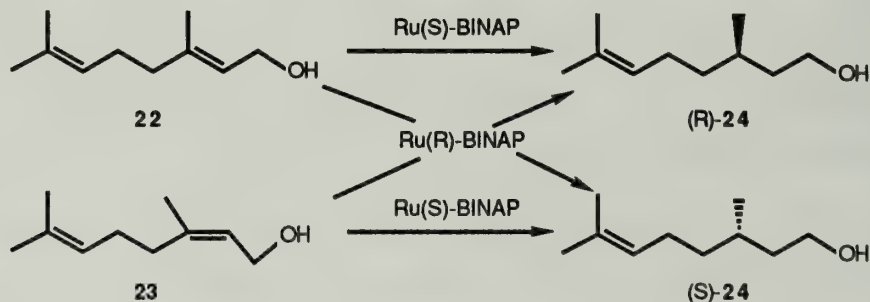
(Rh<sup>I</sup>(DIAMP) or Ru(BINAP)) was used, the two enantiomers reacted at different rates, and only one enantiomer was converted into its hydrogenated product under the reaction conditions (Scheme XI).<sup>26a</sup>

Scheme XI



**Enantioselective hydrogenation of achiral allylic alcohols.** Enantioselective hydrogenation of allylic alcohols with more than one double bond has been addressed by Noyori and coworkers.<sup>27</sup> By comparing two catalysts, BINAP-Rh(I) complex and BINAP-Ru(II) complex, they found that the Ru(II) catalyst afforded high chemical yields and regioselectively hydrogenates the C(2),C(3) double bond (Scheme XII) with 96-99% enantioselectivity.

Scheme XII



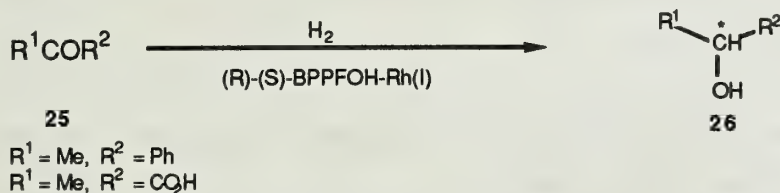
### Hydrogenation of ketones

Increasing attention has been focused on catalytic asymmetric hydrogenation of prochiral carbonyl compounds with certain chiral biphosphine-rhodium catalyst precursors.<sup>28</sup> Chelation is also a key factor in the hydrogenation since simple ketones under the same conditions give low stereoselectivities and poor chemical yield. Hydrogenation of  $\alpha$ -keto esters with a chiral phosphine-rhodium(I) catalyst gave alcohols in high optical



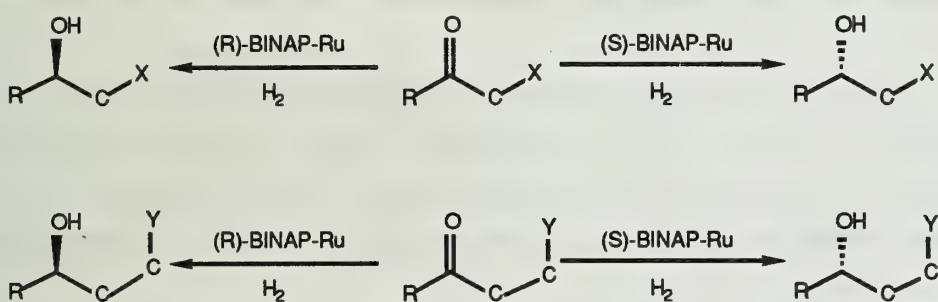
yields (Scheme XIII). Recently Noyori found that the BINAP-Ru dicarboxylate complexes and the halogen containing complexes  $\text{RuX}_2(\text{BINAP})$

#### Scheme XIII



(X=Cl, Br, or I) can serve as excellent catalyst precursors in the asymmetric hydrogenation of  $\alpha$ - or  $\beta$ -functionalized ketones.<sup>14,29</sup> The general scheme of the asymmetric induction is illustrated in Scheme XIV. Only the halogen-

#### Scheme XIV



X, Y = heteroatom, C =  $\text{sp}^2$  or nonstereogenic  $\text{sp}^3$  atom

chelated complexes,  $\text{Ru}(\text{X}_2)(\text{BINAP})$  are efficient in the reactions of oxygen-coordinated (i.e., X or Y=O) hydrogenation. Excellent levels of enantioselection have been observed with a wide range of  $\alpha$ -, or  $\beta$ -functionalized ketones. The results suggest that coordination of the carbonyl oxygen and heteroatom to the Ru atom five- or six-membered chelated ring is an important factor.

#### CONCLUSION

Catalytic homogeneous hydrogenations have been shown to be effective methods for the preparation of a variety of substituted acids and alcohols derivatives. Their high reactivity and stereoselectivity provide an alternative to biochemical methods for asymmetric synthesis.

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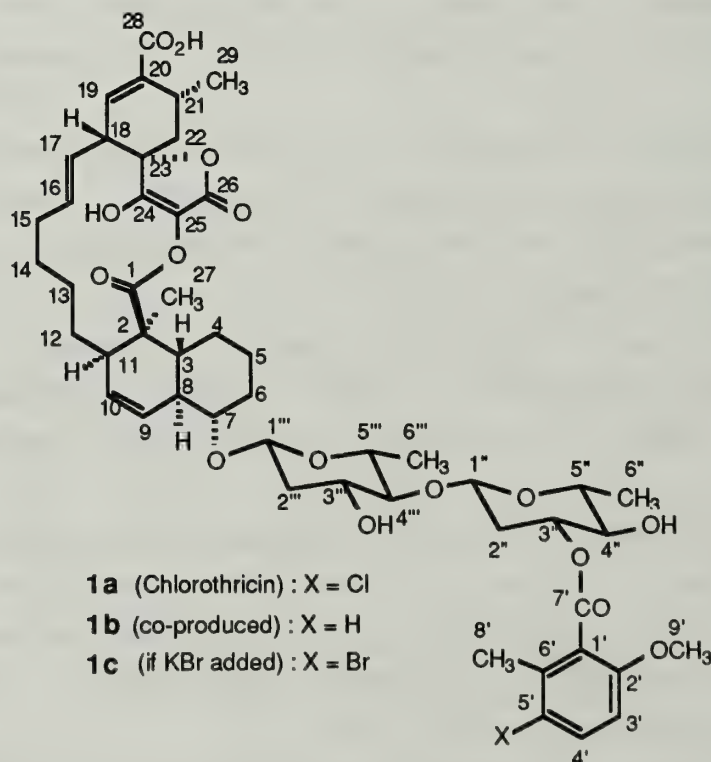
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## STUDIES ON THE BIOSYNTHESIS OF CHLOROTHRICIN

Reported by Erik S. Adams

May 2, 1988

Chlorothricin (**1a**) is a macrolide antibiotic produced by *Streptomyces antibioticus*, Strain Tü 99. Interest in its biosynthesis has been motivated not so much by its antimicrobial activity, since it is active only against gram positive bacteria on synthetic media,<sup>1</sup> as by its novel structure. The macrocyclic lactone, from which the compound receives its macrolide classification, contains a *trans*-decalin system and a tetronic acid unit linked in a spiro fashion to a cyclohexene. In addition, its saccharide component consists of two identical dideoxy sugar units, namely 2-deoxy-D-rhamnose, found in only a handful of antibiotics, such as the olivomycins.<sup>2</sup> Present also is a 6-methylsalicylic acid derivative containing a halogen.



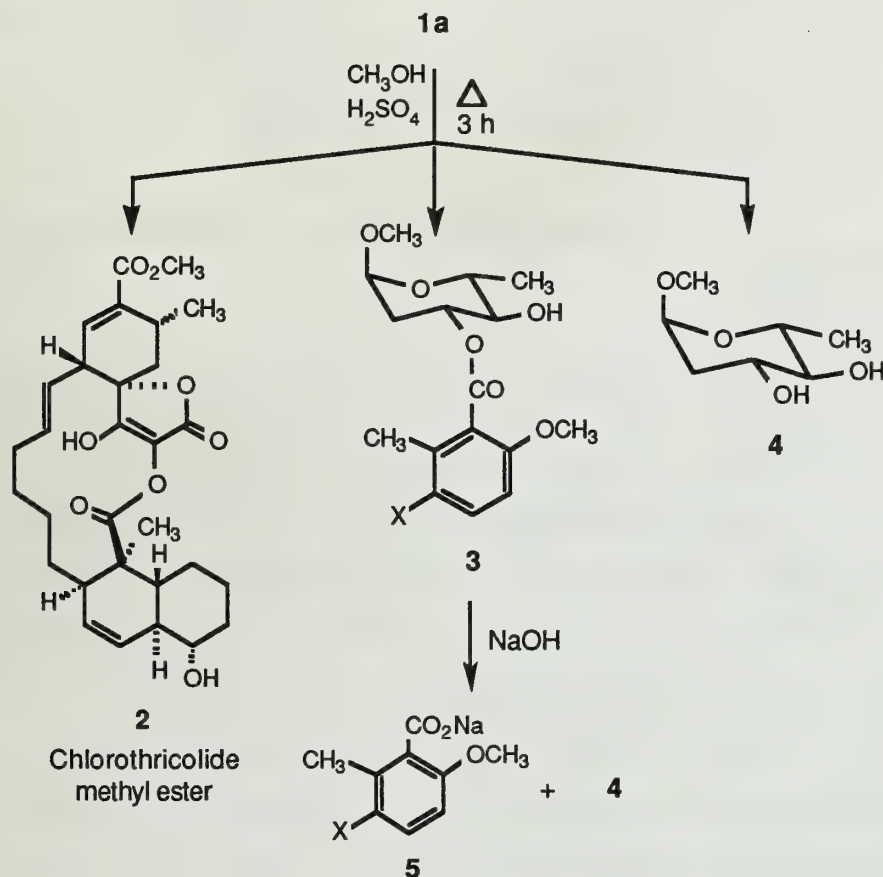
## ANALYSIS OF LABELED CHLOROTHRICIN

Methanolysis of **1a** allowed its separation into the aglycon, chlorothricolide, isolated as the methyl ester (**2**), methyl  $\alpha$ -2-deoxy-3-O-



acyl-D-rhamnoside (**3**), and methyl  $\alpha$ -2-deoxy-D-rhamnoside (**4**).<sup>3</sup> Compound **3** was further degraded to **4** and the chlorosalicylate derivative by hydrolysis in base (Scheme I).<sup>4</sup>

**Scheme I**



Liquid scintillation counting of radioisotopes could therefore be used to determine the incorporation from precursors into the various components of chlorothricin - **2**, **4** and **5**. For studies of  $^{13}\text{C}$  or  $^2\text{H}$  incorporation this degradation also simplified  $^{13}\text{C}$  or  $^2\text{H}$  NMR spectra of the products.

#### INCORPORATION OF ACETATE AND PROPIONATE

Feeding experiments with  $[1-^{14}\text{C}]$ acetate<sup>3</sup> showed consistently good incorporations into chlorothricin, with the majority of the label found in the chlorothricolide methyl ester, **2** (Table 1). The sugar units, **4**, were not labeled by acetate, but the acyl rhamnoside, **3**, did show activity, indicating that acetate was incorporated into the 6-methylsalicylic acid

derivative. Experiments with [2-<sup>14</sup>C]acetate and <sup>14</sup>C-labeled propionate are also shown in Table 1.

**Table I.** Incorporation into **1a** and Analysis of Methanolysis Products

Precursor		Chlorothricin ( <b>1a</b> )	
Name	Specific Activity (mCi/mmol)	Specific Activity (mCi/mmol)	% Incorporation
[1- <sup>14</sup> C]acetate	0.0029	2.91 x 10 <sup>-3</sup>	9.98
[2- <sup>14</sup> C]acetate	0.0096	1.76 x 10 <sup>-3</sup>	3.5
[1- <sup>14</sup> C]propionate	0.0134	0.023	0.15
[2- <sup>14</sup> C]propionate	0.010	0.185	1.8
[3- <sup>14</sup> C]propionate	0.0075	0.233	3.5

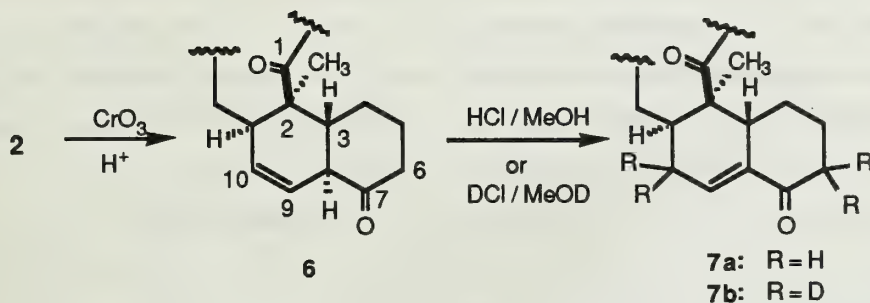
% of Specific Activity of <b>1</b> found in each component			
Precursor	<u>2</u>	<u>3</u>	<u>4</u>
[1- <sup>14</sup> C]acetate	53	26	0
[1- <sup>14</sup> C]propionate	24	11	0
[3- <sup>14</sup> C]propionate	58	33	0

Such labeling patterns are consistent with those found in other macrolides assembled through the polyketide pathway, in which malonyl CoA, derived from the carboxylation of acetyl CoA, is condensed with a growing acyl CoA chain.<sup>5a</sup> Modification of the incomplete or complete poly- $\beta$ -ketone chain may occur by reduction and dehydration, giving the polyketide. The presence of label in the aromatic acyl unit of chlorothricin indicates that this unit is also polyketide derived, as expected.<sup>5b</sup>

The use of <sup>13</sup>C and <sup>2</sup>H labeled precursors required the assignment of <sup>13</sup>C and <sup>1</sup>H NMR spectra. Assignment of the <sup>13</sup>C NMR spectrum<sup>6</sup> was accomplished by first comparing the spectra of **1a** and **2**. Only two of the sp<sup>2</sup> carbon peaks changed upon methanolysis of **1a**, and these were assigned to C-28 and C-19. The remaining carbonyl carbons of **2** at C-1 and C-26 (177.5 and 164.9 ppm, respectively) were identified by their multiplicities and distinguished from each other by chemical shift theory, as was the case for C-24, C-25 and C-20. The remaining four olefinic methine carbon signals were assigned by the procedure shown in Scheme II. This allowed the unequivocal assignments of C-7, C-16 and C-17, the chemical shifts of C-16 and C-17 being unaffected by the derivatization. In addition, studies with model compounds resembling the trans-decalin systems of **2** and **6**, and reduction of the nuclear overhauser effect in C-6 and C-10 when comparing **7b** to **7a** aided in the assignment of other carbons of the trans-decalin unit. Certain signals could not be distinguished, however, such as C-13 and C-14, and these were assigned with

the help of  $^{13}\text{C}$  NMR spectra of **2** derived from  $[^{13}\text{C}]$ acetate feeding experiments.

**Scheme II**



Initial attempts at the analysis of the  $^1\text{H}$  NMR spectrum centered on degradation and derivatization reactions,<sup>7</sup> but were ultimately dependent upon the crystal structure determination.<sup>8</sup> Even so, the  $^1\text{H}$  NMR spectrum was not completely assigned in the structure analysis paper or others, so it must be assumed that unpublished  $^1\text{H}$  NMR studies were conducted later.

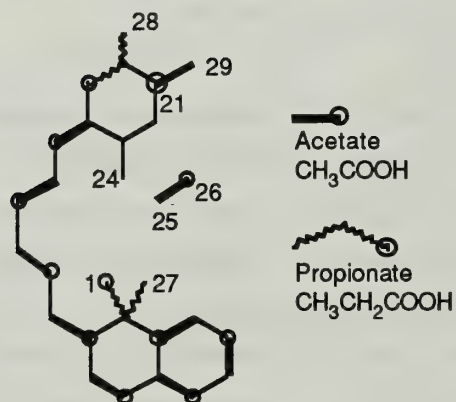
Experiments with  $^{13}\text{C}$ -labeled propionate and  $[^{13}\text{C}_2]$ acetate conclusively demonstrated the polyketide origin of **2** and **5**. Incorporation of  $[1-^{13}\text{C}]$ propionate was found to enhance the  $^{13}\text{C}$  NMR signals of C-1 and C-19, while  $[3-^{13}\text{C}]$ propionate enhanced those of C-27 and C-28. When  $[^{13}\text{C}_2]$ acetate was fed, coupling constants of between 30 and 50 Hz were obtained for carbons 3 through 18, as well as C-21 and C-29, which all appeared as doublets in  $^{13}\text{C}$  NMR spectra. In addition, C-25 and C-26 appeared as doublets superimposed on singlets, with  $^1J_{\text{C-C}} = 91.5$  Hz. Given data from  $^{13}\text{C}$  NMR spectra of **2** derived from the  $^{13}\text{C}$  acetate and propionate feeding experiments, the biosynthetic origins of the aglycon can be summarized as in Scheme III.<sup>4</sup>

Assuming that the acetate corresponding to C-29 and C-21 is the starter unit for polyketide biosynthesis, the incorporation of acetate into C-25/C-26 raises the possibility that the polyketide chain extends from the starter unit, through C-1, to C-26. Baeyer-Villiger oxidation would then insert the oxygen atom between C-1 and C-25.<sup>4,9</sup> Such a pathway is in contrast, however, to the usual pattern of polyketide biosynthesis exhibited by the macrolide antibiotics aplasmomycin and the avermectins. In the former, C-1 (the lactone carbonyl) and C-2 are acetate-derived and are obviously the last unit in the polyketide chain, as the carbons on the "other side" of the lactone ring oxygen are glycerol-derived.<sup>10</sup> In the avermectins, acetate units are

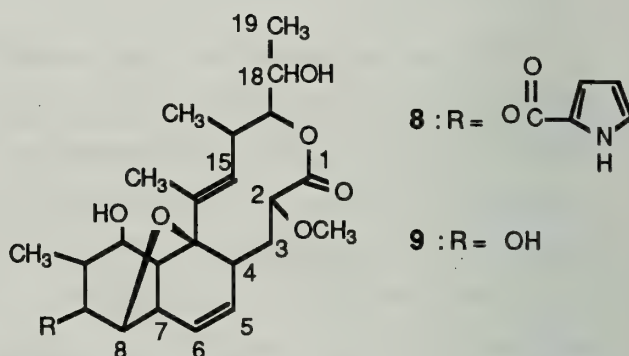


incorporated into carbons on both sides of the lactone ring oxygen, but with opposite orientations. That is, both acetates have C-1 bonded to the ring oxygen. This would lead to the conclusion that the polyketide chain terminates at the lactone carboxyl.<sup>11</sup> Thus, it can be seen in chlorothricin that the relative orientation of the C-25/C-26 acetate to the propionate which labels C-1 allows for the possibility of polyketide chain growth through C-1 to C-26.

Scheme III



Scheme IV



#### FURTHER STUDIES ON THE AGLYCON

In experiments to determine the biosynthetic origin of carbons 22-24, L-[U-<sup>14</sup>C]malic acid and especially [2,3-<sup>14</sup>C<sub>2</sub>]succinic acid were found to be efficient precursors. However, <sup>13</sup>C NMR spectra of **2** derived from feeding experiments with [1,4-<sup>13</sup>C<sub>2</sub>]succinic acid demonstrated that incorporation occurred predominantly at positions enriched by [1-<sup>13</sup>C]propionate. Considering also that [1-<sup>13</sup>C]acetate enriches positions derived from C-1 of propionate,<sup>9</sup> this situation is similar to that found for the macrolide antibiotics nargenicin, (**8**), and nodusmycin, (**9**), shown in Scheme IV.<sup>12</sup> In nargenicin, high incorporations were observed for [2,3-<sup>14</sup>C<sub>2</sub>]succinic acid, and in both nodusmycin and nargenicin, [1-<sup>13</sup>C]acetate labeled "propionate" positions. These results were interpreted to indicate the processing of labeled acetate through the TCA cycle, with conversion of the resulting succinate to propionate via methylmalonyl CoA.<sup>13</sup> Such may also be the case for chlorothricin.

Feeding of [2-<sup>14</sup>C]glycerol also resulted in high incorporations, and [U-<sup>13</sup>C<sub>3</sub>]glycerol was shown by <sup>13</sup>C NMR studies to be incorporated into C-22 to C-



24; acetate- and propionate-derived positions were also labeled due to metabolism of glycerol. Carbons 22 and 24 showed prominent  $^{13}\text{C}$ - $^{13}\text{C}$  couplings, and irradiation of the C-23 multiplet resulted in collapse of the C-22 and C-24 signals into singlets.<sup>4</sup>

To determine the orientation of the glycerol unit within the polyketide framework, (2*R*)-[1,1- $^2\text{H}_2$ ]glycerol (**10**) was administered to cultures of *S. antibioticus* Tü 99. Deuterium NMR spectra of labeled **2** showed deuterium retention in the *pro-R* hydrogen of C-22 (Scheme V). It thus follows that the *pro-R* hydroxymethyl group of glycerol (which becomes C-3 of 3-phosphoglycerate during metabolism) gives rise to C-22, and the *pro-S* hydroxymethyl group labels C-24.<sup>4</sup>

Scheme V

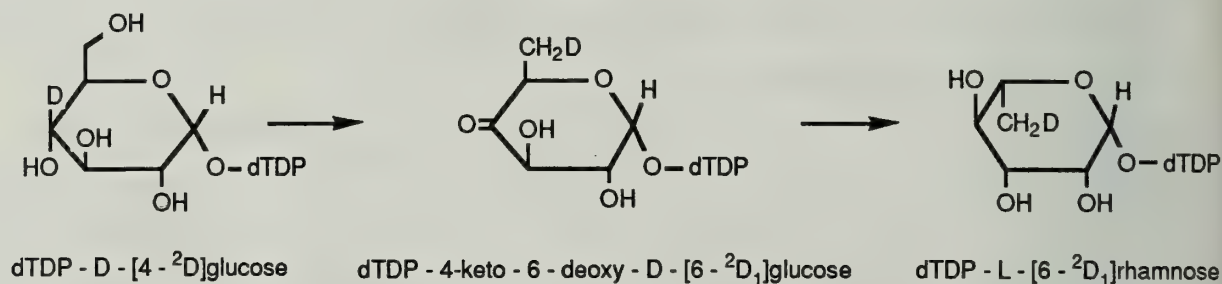


#### Biosynthesis of the Rhamnose Units

D-[U- $^{14}\text{C}$ ]glucose was found to be efficiently incorporated into **1**, with label scattered throughout the entire molecule. It is expected that glucose would be metabolized to acetyl-CoA and thus be incorporated into the aglycon and acyl units, and it seems reasonable that it would be incorporated directly into the rhamnose units. To test this hypothesis, feeding experiments were done with [6- $^{14}\text{C}$ , 6- $^3\text{H}$ ]glucose. [2- $^{14}\text{C}$ , 2- $^3\text{H}$ ]Acetyl CoA derived from this precursor would lose a significant amount of tritium to water upon its entry into the TCA cycle, especially in its condensation with oxaloacetate to give citrate.<sup>14</sup> Thus, it is expected that the aglycon and acyl units would exhibit lower  $^3\text{H}$  retention, relative to  $^{14}\text{C}$  incorporation, than the sugars. This was the case, as incorporation into chlorothricin as a whole exhibited 28%  $^3\text{H}$  retention relative to  $^{14}\text{C}$ , while incorporation into the 2-deoxyrhamnose units showed 83%  $^3\text{H}$  retention. When [6- $^{14}\text{C}$ , 4- $^3\text{H}$ ]glucose was fed, this difference was even more pronounced.<sup>3</sup>

These data suggest the involvement of the glucose nucleotide oxidoreductase reaction. This has been shown in *S. fradiae* to involve the conversion of deoxy-thymidine diphosphoglucose (dTDP-glucose) to dTDP-4-keto-6-deoxyglucose, accompanied by hydride transfer from C-4 to C-6 of glucose,<sup>15</sup> followed by epimerization at C-5 and C-3 and stereospecific reduction at C-4 (Scheme VI).<sup>16</sup> In addition, the dTDP-4-keto-6-deoxyglucose has a hydrogen at C-5 which is obtained from solvent, and the subsequent epimerization of C-3 causes loss of any <sup>2</sup>H or <sup>3</sup>H at this position.<sup>16</sup>

Scheme VI



With this in mind, Mascaretti, et al. investigated the tritium retention in chlorothricin when di-labeled glucose was fed (Table 2). The incorporation of glucose with complete tritium retention at C-2 and C-6 leaves no doubt that "intact conversion" of glucose into 2-deoxy-D-rhamnose is occurring.<sup>9</sup> Note also that the loss of <sup>3</sup>H at C-3 and C-5 and the comparatively better <sup>3</sup>H retention at C-4 are similar to results obtained with L-rhamnose synthesis by dTDP glucose oxidoreductase.

Table II

Glucose labeling pattern	<sup>3</sup> H/ <sup>14</sup> C Activity of precursor	% Tritium Retention	
		Chlorothricin	Methyl α-2-deoxy-D-rhamnoside
6- <sup>14</sup> C, 1- <sup>3</sup> H	1.45	14.4	67.5
6- <sup>14</sup> C, 2- <sup>3</sup> H	1.93	19.6	100.0
6- <sup>14</sup> C, 3- <sup>3</sup> H	1.81	7.1	10.4
6- <sup>14</sup> C, 4- <sup>3</sup> H	2.50	4.8	36.0
6- <sup>14</sup> C, 5- <sup>3</sup> H	3.97	1.0	3.2
6- <sup>14</sup> C, 6- <sup>3</sup> H	2.10	25.7	100.0

Assuming that a similar mechanism is occurring for the synthesis of 2-deoxy-D-rhamnose in chlorothricin, (6R) and (6S)-D-[6-<sup>14</sup>C, 4-<sup>2</sup>H, 6-<sup>3</sup>H]glucose were fed to investigate the stereochemistry of hydride transfer from C-4 to

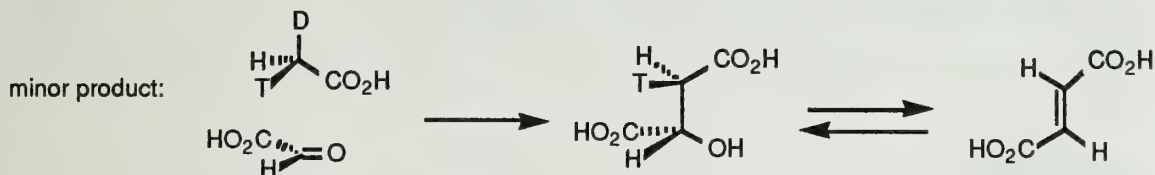
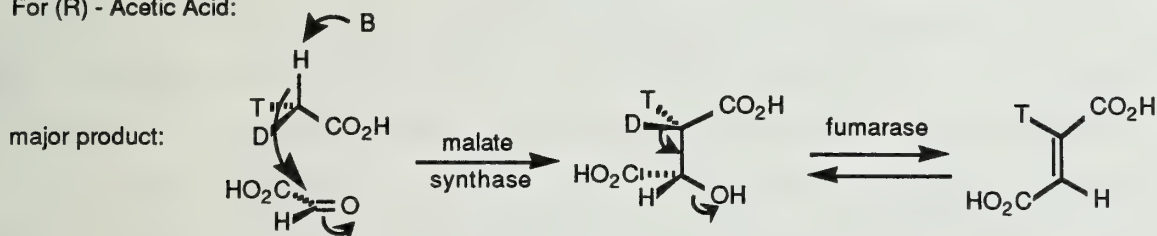
C-6. The labeled methyl  $\alpha$ -2-deoxy-D-rhamnoside obtained by methanolysis was subjected to Kuhn-Roth oxidation to yield chiral acetic acid, with C-2 of the acetic acid originating from C-6 of the sugar.

The chirality of the acetic acid was then determined by the enzymatic method developed by Cornforth and Arigoni,<sup>5c,17,18</sup> (Scheme VII), which depends upon a primary kinetic isotope effect in the malate synthase reaction ( $k_H > k_D > k_T$ ), such that abstraction of T is unlikely, and abstraction of D results in the minor product.

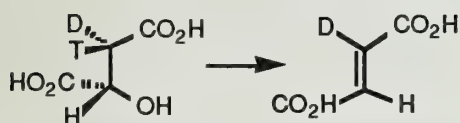
When (6R) labeled glucose was fed, the product showed  $^3\text{H}$  retention of 39% in this analysis, indicating that the 2-deoxy-D-rhamnose was (6S). When (6S)-glucose was fed,  $^3\text{H}$  retention was 60%, indicating an R configuration. Thus, hydride transfer occurs with inversion of configuration at C-6 of glucose. This also demonstrates that hydride transfer was intramolecular, as intermolecular transfer with the relatively large quantities of endogenous, unlabeled glucose present would have resulted in achiral products.<sup>9</sup>

**Scheme VII**

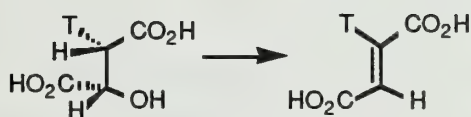
For (R) - Acetic Acid:



For (S) - Acetic Acid:



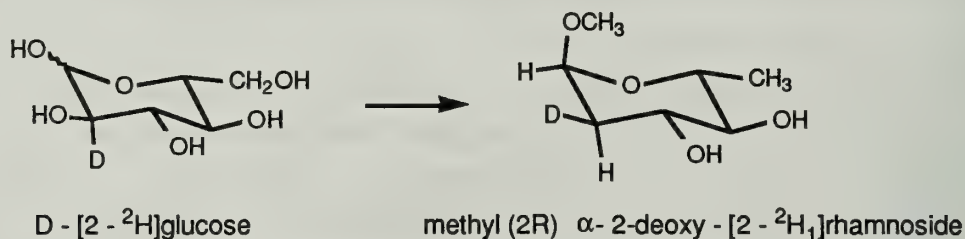
major product



minor product

To obtain information on the fate of the hydrogen at C-2 upon loss of the hydroxyl at that position, [2-<sup>2</sup>H]glucose was fed to obtain methyl α-2-deoxy-D-rhamnoside, which was shown by <sup>2</sup>H NMR to have a deuterium signal at the equatorial position of C-2, but none at the axial position. Its biosynthesis from glucose therefore occurs as shown in Scheme VIII,<sup>4</sup> with reduction at C-2 occurring with inversion of configuration.

#### Scheme VIII



#### CONCLUSION

Studies using di-labeled acetate have conclusively demonstrated the polyketide origin of the chlorothricolide and methylsalicyl portions of chlorothricin. It was also determined, by feeding chiral glycerol, that three of the aglycon carbons are derived from glycerol. Furthermore, NMR studies of the products from acetate, propionate, and glycerol feeding experiments have shown the orientation of these precursors in assembly of the aglycon and acyl moieties. The novel 2-deoxy-D-rhamnose units are biosynthesized from glucose through a mechanism similar to that of L-rhamnose synthesis with dTDP glucose oxidoreductase. The stereochemistry of this conversion was investigated using glucose labeled in such a way as to produce a chiral methyl group at C-6.

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# MECHANISM OF BIOTIN-DEPENDENT CARBOXYLATIONS

Reported by Roopa Rai

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## INTRODUCTION

Biotin is an essential cofactor for a small number of enzymes<sup>1</sup> that have diverse metabolic functions. In general, it serves as a covalently bound "CO<sub>2</sub> carrier" for enzymes which catalyze reactions in which carbon dioxide is attached to an acceptor (carboxylases), a carboxyl group is transferred from a donor to an acceptor (transcarboxylases) or a carboxyl group is removed from a donor (decarboxylases).

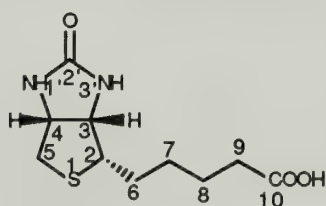
### Overall Mechanism

Biotin-dependent carboxylations occur via two independent partial reactions:



In transcarboxylase, methylmalonyl-CoA is the carboxyl donor, replacing ATP and bicarbonate. Decarboxylases, too, do not require ATP. Instead, reaction (2) proceeds right to left, followed by decomposition with release of carbon dioxide.

(+)-Biotin is the biologically active form in these enzymes. The structure and stereochemistry of the (+)-biotin prosthetic group and a schematic representation of the proposed active site of pyruvate carboxylase are shown in Figure 1. The two partial reactions of



(+)-Biotin

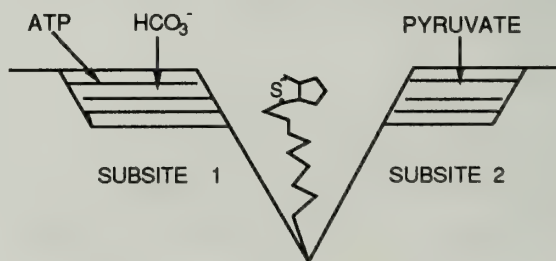


Figure 1

carboxylases and decarboxylases occur at two different sites on the enzyme.<sup>2</sup> The three subunits involved in catalysis are: (a) biotinyl carboxyl carrier protein, (b) biotin carboxylase which catalyzes the first half reaction and (c) carboxyl transferase which catalyzes the second half reaction. Hence,

the carboxylated biotinyl prosthetic group undergoes translocation from the carboxylation site on biotin carboxylase to the transfer site on carboxyl transferase, while remaining attached to the carboxyl carrier protein.<sup>3</sup>

This report will focus on the mechanistic aspects of the two partial reactions (1) and (2). It has been argued that both the carboxylation of biotin and subsequent transfer of the carboxyl group to a substrate go through a stepwise mechanism. Evidence that supports a stepwise mechanism for these reactions, as opposed to a concerted one, will also be discussed.

## THE FIRST HALF REACTION

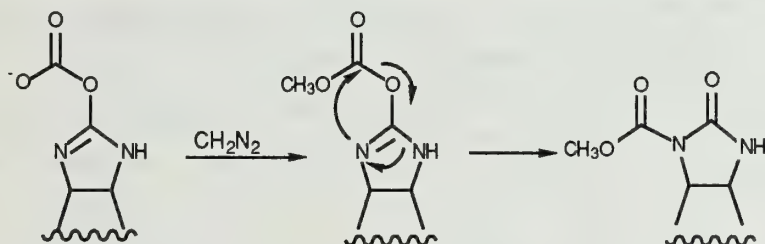
### Bicarbonate involvement

When  $\text{HC}^{18}\text{O}_3^-$  was used to investigate the mechanism of propionyl-CoA carboxylase,<sup>4</sup> one  $^{18}\text{O}$  atom was incorporated into orthophosphate for every two  $^{18}\text{O}$  atoms incorporated into the carboxyl group of the product. Furthermore, there was very slow incorporation when carbon dioxide was the initially labelled species, while bicarbonate was incorporated rapidly. Thus, bicarbonate appears to be the species involved in the carboxylation.<sup>5</sup>

### Site of Carboxylation on Biotin.

Treatment of carboxybiotin with diazomethane gave its dimethyl ester, which was shown by X-ray crystallographic studies<sup>6</sup> to have the methoxycarbonyl group on the 1'-N position of biotin. Since the most nucleophilic site on the ureido ring is the carbonyl oxygen, it was originally argued that perhaps the ureido oxygen was the initial site of carboxylation, but that methylation caused a rearrangement of the carboxyl group to the 1'-N position as shown in Scheme 1.<sup>7</sup> However, in the presence of the biotin carboxylase component of

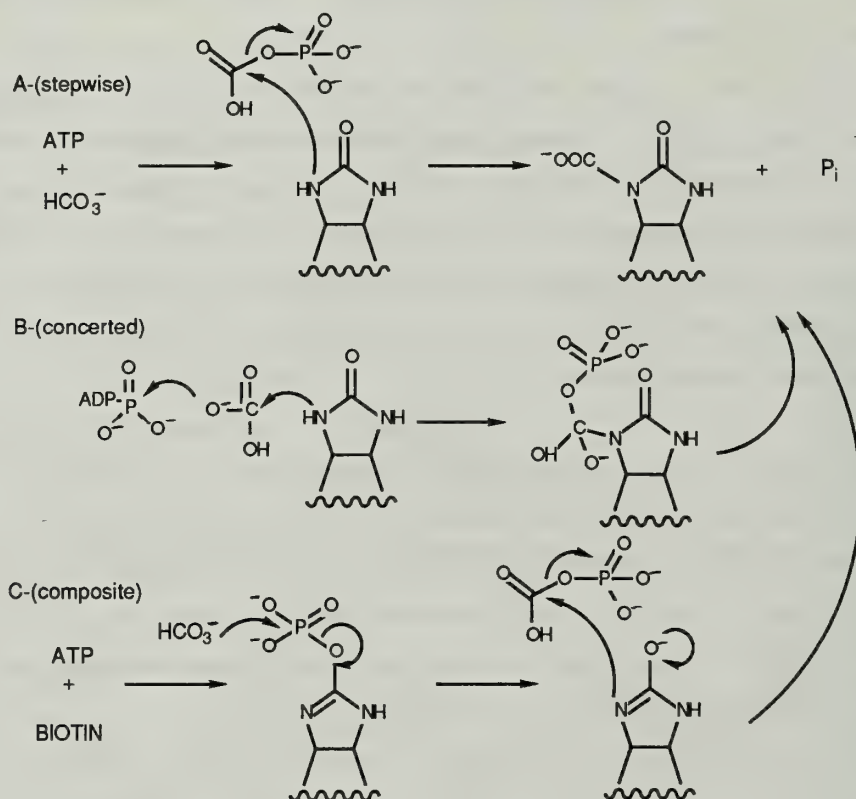
**Scheme I**



acetyl CoA carboxylase, 1'-N-carboxybiotin, ADP and  $\text{P}_i$  gave ATP, thereby suggesting that the 1'-N carboxylated species is the one involved in catalysis.<sup>5</sup>

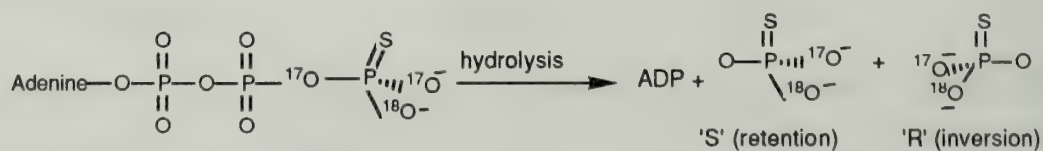
There are three suggested mechanisms for the formation of 1'-N-carboxybiotin (Scheme II). The stepwise mechanism (A, Scheme II), involves

initial substrate activation and the formation of a distinct carboxyphosphate intermediate. In the concerted mechanism (B, Scheme II),  
**Scheme II**



carboxylation of biotin occurs concomitantly with the cleavage of ATP, without the formation of a kinetically significant intermediate. Lastly, the composite mechanism involves initial activation of biotin to its enol tautomer as shown in C, Scheme II. Experiments with enolic biotin models which mimic O-phosphobiotin seem to support the composite mechanism, in which phosphorylation of the ureido oxygen enhances the nucleophilicity of the 1'-nitrogen.<sup>10</sup> However, model compounds are not always reliable indicators of the activity in the environment of an enzyme.

To narrow down the mechanistic possibilities, chicken liver pyruvate carboxylase was studied<sup>7</sup> using chiral ATPγS (Scheme III). The  
**Scheme III**

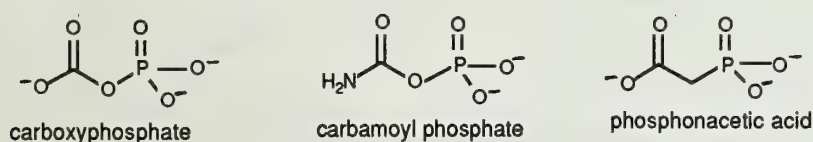




stereochemical fate of the inorganic thiophosphate produced after ATP hydrolysis was studied. The hydrolysis of ATP occurred with overall inversion of configuration at phosphorus. Since the composite mechanism (C, Scheme-II) would involve two direct transfers to phosphorus (each with inversion), and thus, would proceed with overall retention of configuration, the composite mechanism was ruled out.

The stepwise mechanism would involve a carbonic phosphoric anhydride intermediate. Studies with analogs of this intermediate<sup>5</sup>, (Scheme IV), indicate that carboxyphosphate is an intermediate involved in the

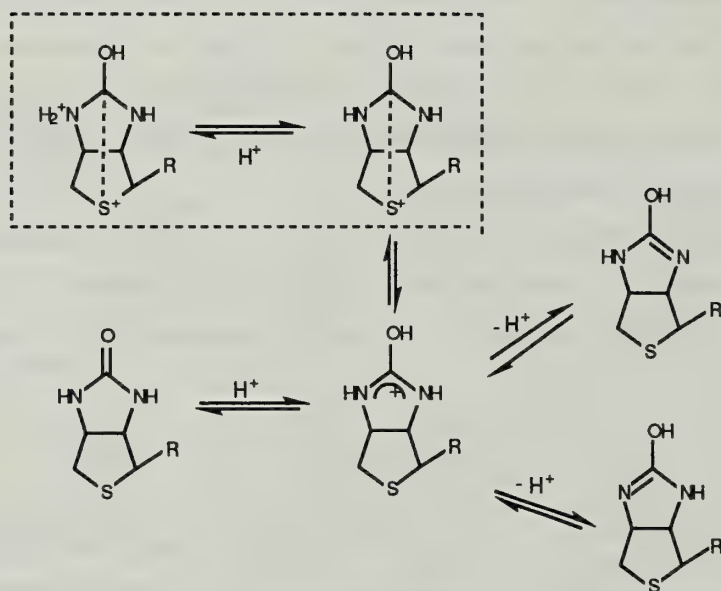
#### Scheme IV



reaction, thus supporting the stepwise mechanism. In these studies, ADP was phosphorylated to ATP from carbamoyl phosphate in a reaction catalyzed by acetyl CoA carboxylase from *E. coli*. Also, phosphonacetic acid was a potent inhibitor of pyruvate carboxylase. Furthermore, in the absence of bicarbonate and  $Mg^{2+}$ , there was no ATP- $[^{14}C]$ ADP exchange and the ATP- $^{32}P_i$  exchange reaction required  $Mg^{2+}$ , ADP and bicarbonate.<sup>5</sup> More evidence for the involvement of a carboxyphosphate intermediate came in recent studies, in which biotin carboxylase from *E. coli* was incubated with ATP in the absence of biotin and bicarbonate-dependent ATP hydrolysis was observed,<sup>11</sup> suggesting that the first step in the stepwise sequence can take place even without biotin.

If the stepwise mechanism were operating, the enzyme should have a way of activating the relatively non-nucleophilic 1'-N position so that it could attack the carboxyphosphate intermediate. The implications of kinetic studies<sup>12</sup> of acid catalyzed NH exchange on (+)-biotin and model compounds are shown in Scheme V, where the pathway enclosed in dashed lines is available only for sulfur containing compounds. In short, it was proposed that sulfur increases the nucleophilicity of the 1'-nitrogen by transannular bonding to the carbonyl carbon of biotin. X-ray studies<sup>13</sup> of biotin and its derivatives reveal bond lengths of C2'=O, C2'-N1' and C2'-N2'

Scheme V



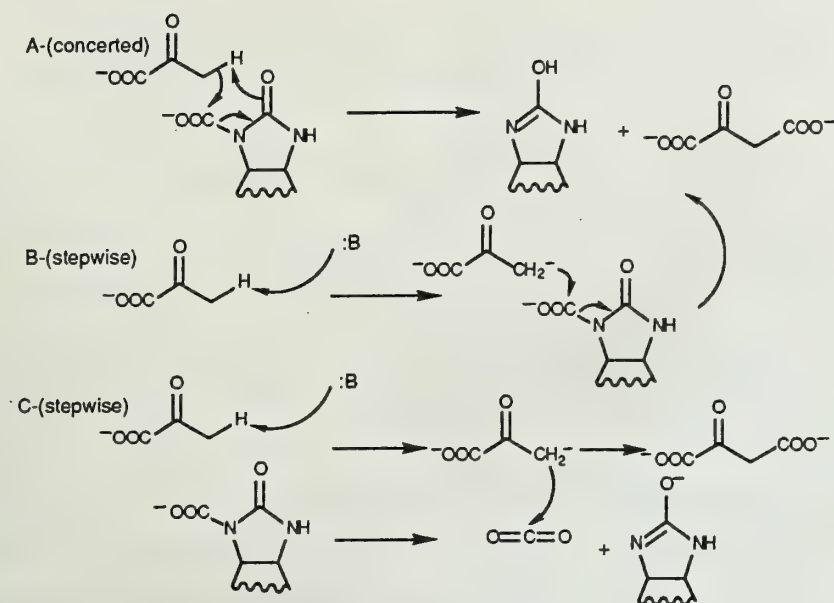
which suggest that the uriedo ring system is substantially polarized and therefore inclined towards activation to the enol tautomer.

#### THE SECOND HALF REACTION

The three proposed pathways for the transfer of carbon dioxide from carboxybiotin to substrate are shown in Scheme VI. A is a concerted mechanism, while B and C are both stepwise mechanisms, differing in whether the carboxyl group is free or biotin-bound.

Biotin-dependent carboxylations proceed with retention of configuration at the carbon center undergoing carboxylation. When these carboxylations were carried out in  $^3\text{H}_2\text{O}$ , no  $^3\text{H}$  was incorporated into the substrate, and the rate of tritium washout from tritiated substrate was identical to the rate of the overall reaction. This evidence<sup>1,14</sup> was taken to support a concerted type of mechanism (A, Scheme VI). However, the stepwise mechanisms (B, C, Scheme VI) could not be ruled out on this basis, because the reaction could be occurring within a solvent cage, or the enzyme may be holding the substrate in a fixed conformation, causing the reaction to be stereospecific. Besides, model studies<sup>15</sup> have suggested that carboxybiotin is stable to nucleophilic attack, and hence, it seemed unlikely that merely aligning the carboxybiotin unit to the acceptor (A, Scheme VI) would result in transfer of the carboxyl group. Crystallographic studies<sup>13</sup> of the intermolecular interactions in the structure of 1'-N-methoxycarbonyl biotin methyl ester

Scheme VI



reveal that the ureido oxygen of one molecule is 3.1 Å from the methyl carbon at the terminus of the methyl esterified valeryl side chain of a symmetry related molecule (Figure 2). In a space filling model, the van der Waals contacts seem to lock the

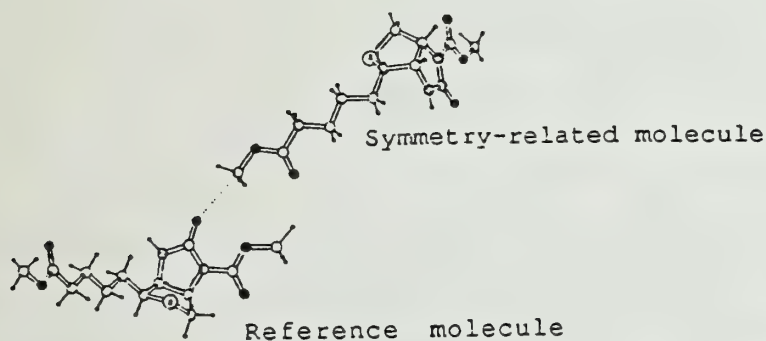
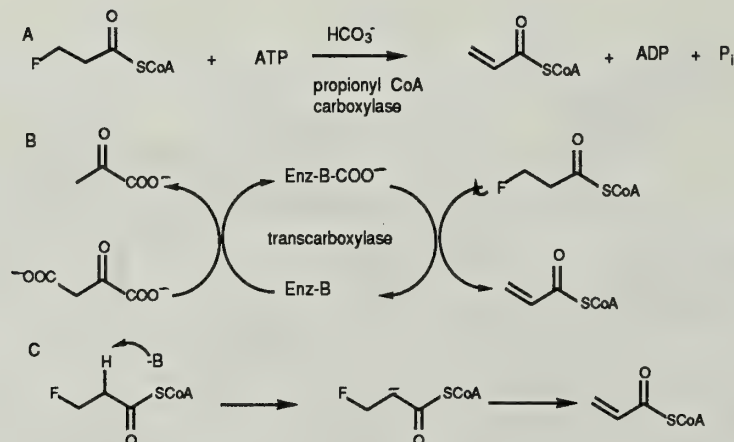


Figure 2

methyl group with respect to rotation. This may provide a structural basis for the observed stereospecificity without invoking a concerted mechanism.

Stubbe, et al.<sup>16</sup> studied carboxylation reactions of transcarboxylase and propionyl-CoA carboxylase (A, B, Scheme VII) using  $\beta$ -fluoropropionyl CoA as substrate. No carboxylation products were isolated and elimination proceeded at approximately the same rate as normal carboxylation reactions. Carbanion formation required prior formation of carboxybiotin. This explained why the rate of release of  $^3\text{H}$  from tritiated substrate was identical to the overall reaction rate. The proposed mechanism (C, Scheme VII), indicates that deprotonation of the substrate can occur without concomitant

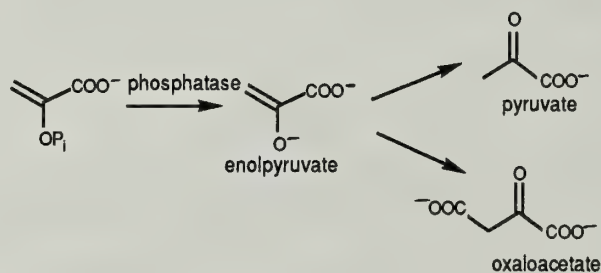
## Scheme VII



carboxylation, thus arguing against a concerted mechanism (A, Scheme VI).

Kuo and Rose<sup>17</sup> studied the conversion of pyruvate to oxaloacetate, catalyzed by pyruvate carboxylase. They reasoned that, in the case of a stepwise mechanism, enzymes that carboxylate pyruvate should be able to convert enolpyruvate to pyruvate and oxaloacetate (Scheme VIII).

## Scheme VIII



Stereospecific ketonization to pyruvate occurred, but only a negligible amount of the carboxylated product was detected. Proton removal from pyruvate is partially rate limiting, hence a true intermediate should partition both back to pyruvate and forward to oxaloacetate. Whether there was a distinct intermediate in the reaction or a transition state with a fleeting existence seemed to be still open to question.

Knowles, et al.<sup>18</sup>, have used the double isotope fractionation method<sup>19</sup> for transcarboxylase analysis (Figure 3). The reaction catalyzed by transcarboxylase involves the breaking of a C-H bond and the making of a C-C bond. Experiments have indicated both <sup>13</sup>C and <sup>2</sup>H primary isotope effects (A, D, Figure 3). However, the <sup>13</sup>C primary isotope effect using <sup>2</sup>H substrate was less than the corresponding value using <sup>1</sup>H substrate. This was expected



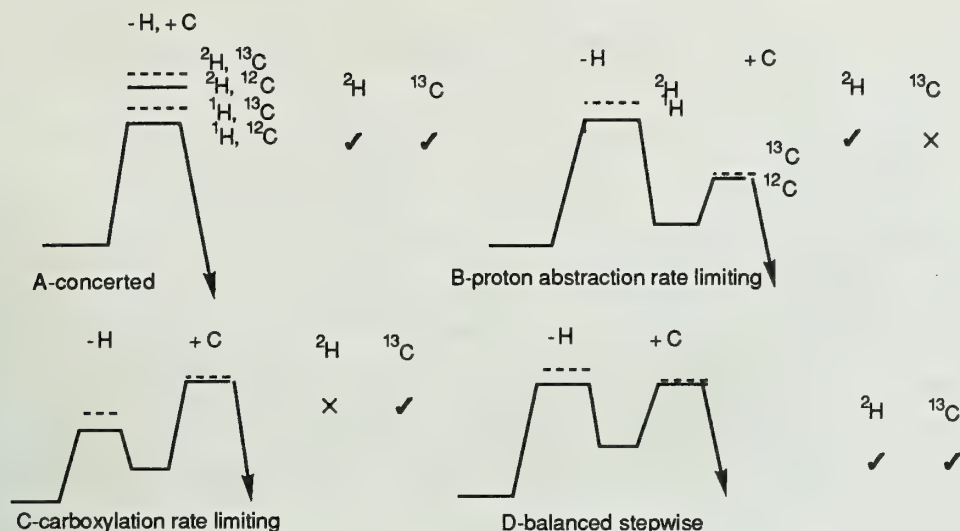


Figure 3

if the stepwise mechanism were operating.

## CONCLUSION

In the first partial reaction, biotin gets carboxylated. Although biotin does not play a direct role in the formation of the carboxyphosphate intermediate, it seems to stimulate the process. In short, it is possible that biotin reorients the ATP and bicarbonate binding sites, so as to facilitate immediate transfer of the carboxyl group from the unstable carboxyphosphate, which might otherwise hydrolyze. Therefore the evidence points to the fact that bicarbonate is the species involved in the carboxylation, and that the reaction occurs in a stepwise manner.

The second partial reaction involves the carboxylation of a substrate by carboxybiotin. From the studies discussed, it is evident that this carboxylation occurs through a stepwise mechanism. However, whether free or enzyme-bound carbon dioxide is involved in the process, seems to be still open to question. More work in this field would help resolve the ambiguities that remain and shed more light on the mechanism of biotin-dependent carboxylations.

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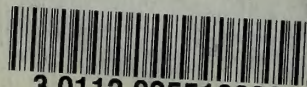








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